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HISTOLOGIC EVIDENCE OF DAMAGE TO THE BRAIN IN MONKEYS TREATED WITH METRAZOL AND INSULIN

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In 1937, having had occasion to observe psychotic patients being treated with insulin and metrazol, we were impressed by the signs of shock and damage to the central nervous system incident to such treatment. The great majority of the patients showed signs of involvement of the pyramidal tracts during the insulin coma or the metrazol seizure, and these signs occasionally remained even after consciousness had completely returned. In addition, various other persistent, and apparently permanent, abnormal neurologic signs were observed, such as absence of the knee jerk, ptosis, strabismus and loss of pupillary accommodation to near objects.

As a result of these observations we undertook to determine what damage to the central nervous system might be produced by similarly administering insulin and metrazol to monkeys.

METHODS AND MATERIAL

The studies were limited to adult Macacus rhesus monkeys, of which three groups were used.

GROUP 1.—Normal Control Animals: Complete serial sections of the brains of 2 normal animals were available in which the entire cerebral vascular bed had been injected with india ink, as described later, and the thinner sections stained with thionine. The third normal control animal was killed under dial anesthesia by opening the chest and severing the aorta. One half of the brain was fixed in 95 per cent alcohol for Nissl stains. The other half was fixed in dilute solution of formaldehyde U. S. P. (1:10) for fat, astrocyte, microglia and oligodendroglia stains.

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GROUP 2.—Metrazol Series: One animal was killed by a massive, divided dose of metrazol. Four other animals were subjected to repeated metrazol convulsions during a period of several weeks.

GROUP 3.—Insulin Series: Six animals were killed after induction of a single coma, ranging from three and a half to twenty-two hours in duration. The remaining 6 animals were subjected repeatedly to hypoglycemic coma during a period of several weeks.

METRAZOL EXPERIMENTS (TABLE 1)

Method.—Metrazol in 10 per cent aqueous solution was injected via the thigh veins. The quantity required to produce a seizure varied from 0.4 to 1.0 cc. For the first injection 0.4 cc. was given; this was increased by 0.1 cc. steps until a convulsion resulted. The later convulsant dose was sometimes larger, as some of the animals seemed to acquire a tolerance to the drug. The resulting seizure was similar to that seen in the human subject. About ten seconds after the injection a tonic seizure developed, lasting ten to twenty seconds, followed a few seconds later by a clonic stage. The clonic stage lasted ten to twenty-five seconds, after which the animal became apneic and cyanotic. After this stage the animal lay on the floor of the cage in a stuporous condition. Occasionally spasmodic twitching of the muscles and jerks of the extremities occurred. Within ten to fifteen minutes after the injection of the drug the animal was up climbing about the cage. We

TABLE 1.—*Data on Monkeys Which Received Metrazol*

Animal	Number of Convulsions	Duration
"Acute metrazol"	8	4½ hours*
1402	15	21 days
1404	21	30 days
1473	45	89 days
1474	48	86 days

* The animal died, and the brain was immediately removed. The remaining animals were killed.

never witnessed a delayed seizure in any of our animals, although such may have occurred in our absence. Except for the acute metrazol monkey, which received several injections within a four hour period, none of the metrazol animals died as a result of the convulsions. The animals had on an average 3 or 4 seizures a week.

The animals were killed under dial anesthesia on the first or second day after the last injection of metrazol. In animals in which the cerebral vascular bed was to be injected the animal was killed by the injection material. In animals in which the cerebral vascular bed was not injected the animal was killed by opening the chest and severing the aorta; the brain was immediately removed and placed in alcohol. For a detailed description of the method of injection the reader is referred to a previous article.[1] Briefly, a mixture of india ink and 5 per cent gelatin at a temperature of 40 C. was injected via the ascending aorta (the chest having been previously opened and the animal kept alive with artificial respiration) under a known pressure of 110 to 130 mm. of mercury. The descending aorta and brachial arteries had been previously clamped to direct the india ink only into the head. After the ink and gelatin had had a chance to set, the head was removed and placed in dilute solution of formaldehyde U. S. P. (1:10) to allow the brain to

1. Finley, K. H.: The Capillary Beds of the Paraventricular and Supra-Optic Nuclei of the Hypothalamus, J. Comp. Neurol. **71**:1-19 (Aug.) 1939.

harden before it was removed. The brain was then carefully removed to prevent distortion of cortical capillaries. It was then washed and run up through alcohols for embedding in pyroxylin. Before the embedding, six frontal sections were made through the brain, all blocks being embedded for complete serial sections if necessary. Sections were cut at 25, 35, 75, 150 and 250 microns and kept in serial order. The 25 and 35 micron sections were stained with thionine, while the thicker sections were mounted unstained for study of the vascular tree. The sections from alcohol-fixed portions of the uninjected brains were cut at 25 microns and stained with thionine by the Nissl technic. The formaldehyde-fixed portions were used in stains for microglia and oligodendroglia (Hortega silver carbonate method) and for Cajal preparations and fat stains.

Results.—Acute Metrazol Monkey: This animal was given 4.5 cc. of a 10 per cent solution of metrazol intravenously in divided doses during a period of four and a half hours. As a result of these injections the animal had 8 major seizures. It was allowed to recover after each injection except the last, which was given only ten minutes after the previous convulsion. The animal died ten minutes after the last injection.

Post mortem, the brain grossly showed merely venous engorgement, with some unevenness in color of the cut surfaces of the cortex. Microscopically, in numerous scattered areas the ganglion cells, both large and small, were seen to be acutely swollen (Nissl stain). No vacuolation of the ganglion cells was observed. The cells of the basal ganglia, cord and medulla appeared normal, as did the glia elements throughout the brain. The blood vessels were not injected in this animal, but no vascular abnormalities were observed in the Nissl preparations.

Monkey 1402: This animal received 15 injections of from 0.5 to 0.8 cc. of a 10 per cent solution of metrazol intravenously during a period of twenty days. After each but one of these injections the animal had a typical tonic and clonic seizure. On the day after the last injection the animal was killed by the intra-aortic infusion of the mixture of india ink and gelatin in the usual way.

Grossly no pathologic changes were evident. Microscopically one saw scattered throughout the neocortex small areas, measuring about 1 mm. in diameter, in which no ganglion cells appeared (fig. 1 *A* to *C*). In one such area (fig. 1 *A* and *B*) ink was seen to have leaked out into the parenchyma. This would appear to be of pathologic significance, as the extravasation of ink particles in numerous other experiments undertaken by one of us (K. H. F.) on both monkeys and cats has been observed only in areas in which pathologic lesions could be clearly demonstrated by other methods. No pathologic changes were observed in this animal in the basal ganglia, cord or medulla or in the glia anywhere in the brain.

Monkey 1404: This monkey was given 21 injections of from 0.5 to 0.7 cc. of a 10 per cent solution of metrazol intravenously during a period of twenty-nine days. After each injection the animal had a typical tonic and clonic seizure. On the day after the last injection the animal was killed by the intra-aortic infusion of the mixture of india ink and gelatin in the usual way.

Grossly no pathologic changes were evident. Microscopically one again saw scattered through the neocortex small areas, measuring about 1 mm. in diameter, in which no ganglion cells appeared (fig. 1 *D*). No regions were seen in which ink had extravasated from the blood vessels in this brain. No pathologic changes were observed in the basal ganglia, cord or medulla or in the glia elements anywhere in the brain.

Monkey 1473: This animal received 45 injections of from 0.4 to 0.7 cc. of a 10 per cent solution of metrazol intravenously during a period of eighty-six days. After each injection the animal had a typical tonic and clonic seizure. Three days after the last injection the animal was killed and its brain removed for study.

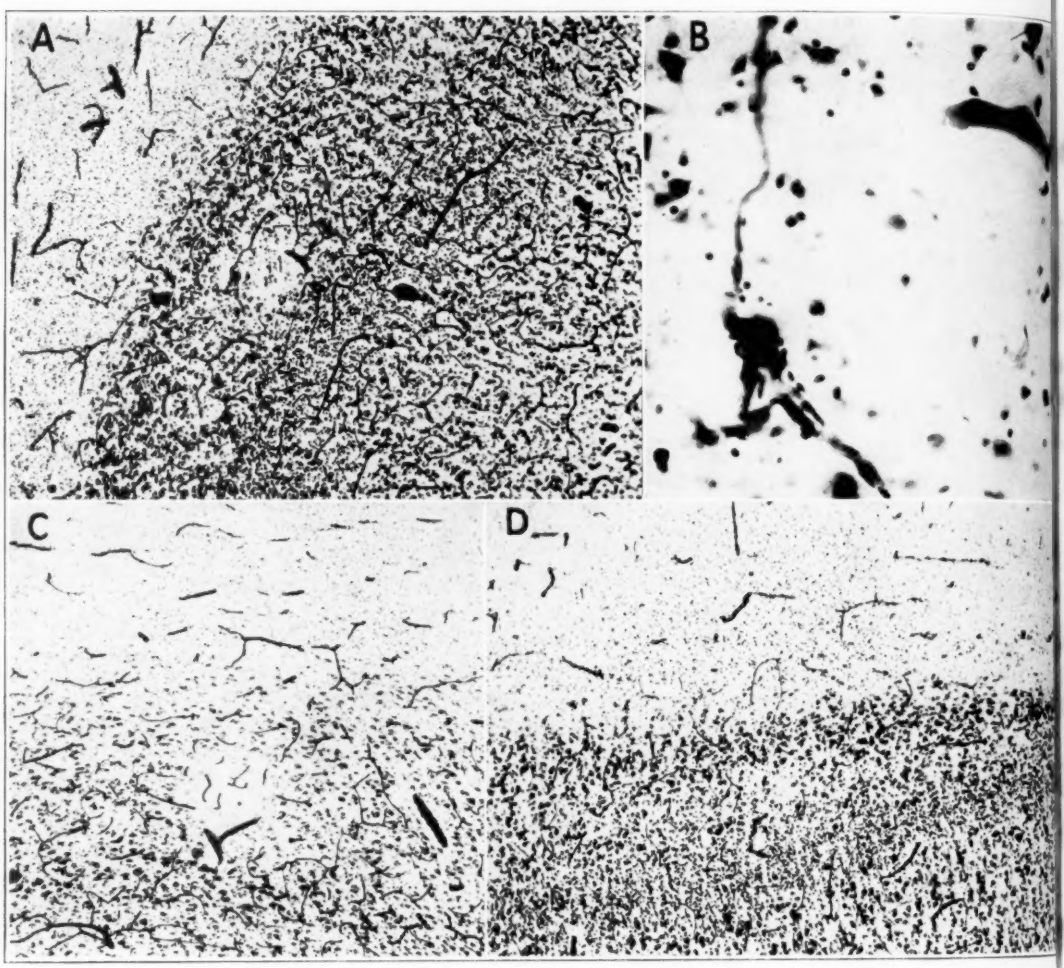

Fig. 1.—Lesions in animals subjected to repeated metrazol convulsions. India ink injections; thionine stain.

A, a small focus in the fifth cortical layer in which the nerve cells have been destroyed. Fifteen seizures; × 60.

B, enlargement of the lesion in *A*, showing ink particles outside a capillary and small vessel, interpreted as evidence of vascular damage. × 290.

C, a small lesion in the sixth cortical layer in which the nerve cells have been destroyed. Fifteen seizures; × 60.

D, a small focus in the fifth cortical layer in which the nerve cells have been destroyed. Twenty-one seizures; × 60.

Grossly no pathologic changes were evident. Microscopically ganglion cells of the cortex, basal ganglia, cord and medulla appeared essentially normal. In the Nissl sections there was clear evidence of astrocytic reaction, however, as shown by a generalized increase in the number of astrocytic nuclei, which was readily detectable in many places in the cortex, and also by the occurrence of clumps of astrocytic nuclei (fig. 2), which were not to be seen in the control brain. This evidence of astrocytic reaction was confirmed by study of the Cajal sections, in which the astrocytes could be seen in various stages of amitotic division in many places in the cortex (fig. 3 *B* and *C*). These zones of reaction were not strictly limited to the gray matter, but often extended slightly into the adjacent white matter. In the Nissl sections there was only suggestive evidence of microglial reaction, but in the Hortega sections in places in the cortex the

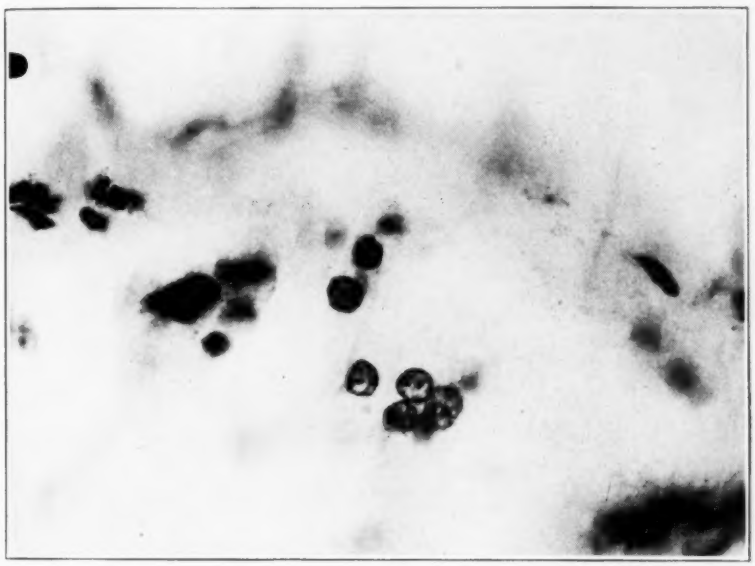

Fig. 2.—A nest of young astrocytic nuclei in the first cortical layer of the brain of an animal with 45 metrazol seizures. × 760.

microglia cells were seen to be increased in number and mildly hypertrophied (fig. 4 *B*). No pathologic reaction in the oligodendroglia was observed. The blood vessels were not injected in this animal, but showed no pathologic changes in the Nissl sections.

Monkey 1474: This animal received 48 intravenous injections of from 0.4 to 1.0 cc. of a 10 per cent solution of metrazol during a period of eighty-three days; after each injection there was a typical tonic and clonic seizure. On the third day after the last seizure the animal was killed by the intra-aortic injection of the india ink and gelatin mixture.

Grossly no pathologic changes were evident. Microscopically one saw scattered throughout the neocortex small areas in which no ganglion cells appeared, similar to areas shown in figure 1 *A* to *D*. In one such area, similar to that shown in figure 1 *A* and *B*, ink was seen to have leaked out into the parenchyma. No other

pathologic alterations of the ganglion cells themselves were observed. In places in the cortex there was clumping of the astrocytic nuclei, similar to that shown in figure 2. Since this was an injected preparation, it was not possible to use any special glia stains. There was no evidence in the Nissl preparations of pathologic alterations of the microglia or the oligodendroglia.

Summary and Comment on Anatomic Changes in the Brains of Animals Which Received Metrazol.—In the brain of the animal that was killed by repeated large doses of metrazol we observed only abnormal swelling of many of the nerve cells, with homogenization of the Nissl substance. We believe that this was due to the toxic effect of the massive doses of metrazol which the animal received and/or the several

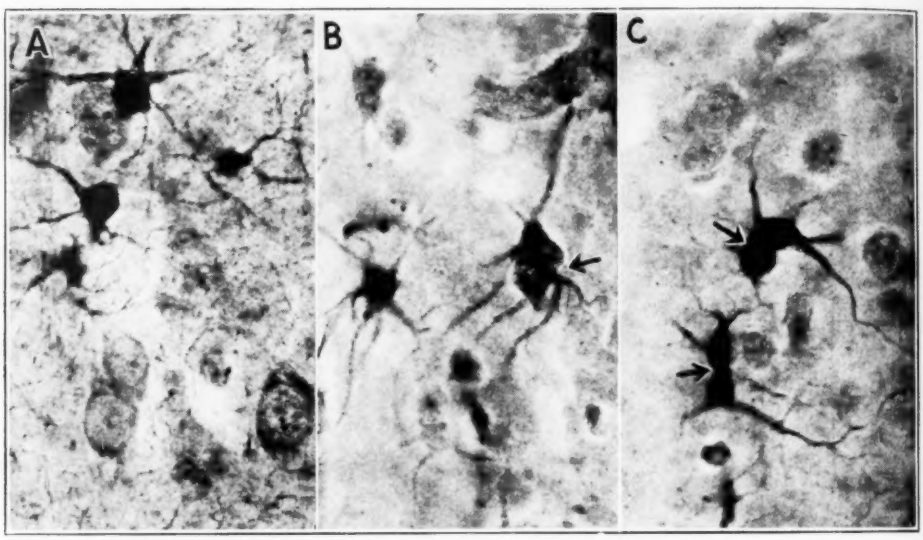

Fig. 3.—*A*, astrocytes in the cortex of a normal control monkey. *B* and *C*, young astrocytes in stages of amitotic division, showing beginning separation of the daughter cells (arrow) in an animal that had had 45 metrazol convulsions. Notice the paler and more vesicular character of the cell bodies and processes, as compared with those in the normal animal.

Cajal gold chloride stain; × 585.

severe prolonged seizures which resulted. We found no evidence of gross or microscopic hemorrhages in this brain.

In the brains of the 4 animals which received repeated injections of metrazol during the course of several weeks we observed essentially two types of pathologic change. The first consisted of small areas in the cortex from which nerve cells were absent and in which there was sometimes definite evidence of vascular damage. These areas may have resulted from small hemorrhages. The second consisted of mild astro-

cytic proliferation in scattered portions of the cortex. Liebert and Weil [2] described evidences of glial proliferation in the brains of rabbits subjected to a series of metrazol convulsions, but neither they nor Strecker and his co-workers [3] noted the focal areas of vascular damage which we observed.

In the brains in which the entire capillary network was injected there were irregular areas scattered throughout the cortex where the capillaries were constricted, producing an irregularly mottled appearance in the thick, unstained sections. We are not sure enough of the

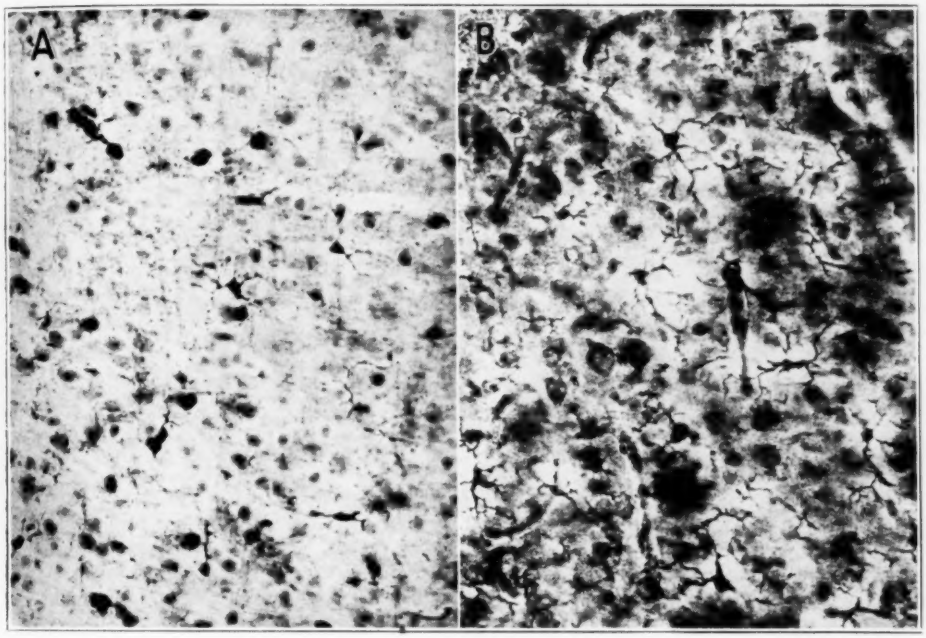

Fig. 4.—*A*, microglia in the cortex of a normal control monkey. *B*, microglia in the cortex of an animal which had had 45 metrazol convulsions. The number of microglia cells is increased, and their processes are longer and coarser; they are the hypertrophic microglia cells described by Penfield.

Hortega silver carbonate stain; thickness 15 microns: × 290.

significance of this observation to lay any particular stress on it, although the several normal injected brains at our disposal did not show it.

2. Liebert, E., and Weil, A.: Histopathology of the Brain Following Metrazol Injections, Elgin State Hosp. Papers **3**:51-57 (Jan.) 1939.

3. Strecker, E. A.; Alpers, B. J.; Flaherty, J. A., and Hughes, J.: Experimental and Clinical Study of Effects of Metrazol Convulsions, Arch. Neurol. & Psychiat. **41**:996-1003 (May) 1939.

Dreszer and Scholz,[4] using the Pickworth and Slonimsky-Cunge capillary-staining methods, found changes in the caliber of the capillary network in the brains of cats that had been given metrazol both in single and in repeated doses.

SINGLE INSULIN COMA EXPERIMENTS (TABLE 2)

Method.—Six adult Macacus rhesus monkeys are included in this series. Each received sufficient insulin intramuscularly to produce and maintain coma for the length of time indicated in table 2. Details of individual doses will be found in the brief protocol accompanying the description of the pathologic changes observed in the brain of each animal. All the animals except monkey Ac-A were observed continuously during the time from injection to death. It is possible that monkey Ac-A recovered from coma for a time during the several hours when it was not under direct observation and then relapsed into coma, so that the figure (twenty-two hours) given in table 2 represents the maximum possible duration of coma. Monkey Ac-A, like all the other animals in the series, was under direct observation at the time of death.

TABLE 2.—*Data on Monkeys Killed After a Single Insulin Coma*

Animal	Duration of Coma, Hours	Comment
Ac-I	3½	Killed
Ac-II	3½	Died*
Ac-M	4½	Killed
Ac-III	9⅓	Died*
Ac-IV	14	Died*
Ac-A	22	Died*

* The brain was removed immediately after death.

The brain of each animal was removed promptly after death and sectioned grossly before fixation. In the cases of monkeys Ac-M and Ac-A the entire brain was fixed in 95 per cent alcohol, embedded in pyroxylin and stained with thionine in the usual manner. In the cases of the other animals a few pieces of the brain tissue from various regions were fixed in dilute solution of formaldehyde U. S. P. (1:10) and stained for fat (scarlet red and alum hematoxylin) and for microglia (Hortega silver carbonate method), while the rest of the tissue was fixed in alcohol and stained with thionine, as already described. From the brains of monkeys Ac-III and Ac-IV sections stained by the Hortega silver carbonate method to demonstrate oligodendroglia were also prepared.

Results.—Monkey Ac-I: This animal was given 16 units of insulin intramuscularly while in a fasting condition. Three and one-half hours after it had lapsed into coma it was killed by severing the cervical portion of the cord, and the brain was removed for study.

Grossly no pathologic changes were evident. Nissl sections showed swollen ganglion cells in regions scattered throughout the cortex. Since a similar appear-

4. Dreszer, R., and Scholz, W.: Experimentelle Untersuchungen zur Frage der Hirndurchblutungsstörungen beim generalisierten Krampf, Ztschr. f. d. ges. Neurol. u. Psychiat. **164**:140-161, 1939.

ance of the small cells in the second and third cortical layers was observed in places in the brain of the control animal, we believe that these apparently swollen cells are of doubtful pathologic significance. No clear evidence of pathologic change was seen in the ganglion cells of the basal ganglia, cerebellum, cord or medulla or in the glia elements anywhere in the brain (Hortega and Nissl stains). The blood vessels were not injected in this animal, but they showed no evidence of pathologic change in the Nissl setions. Stains for fat revealed nothing abnormal.

Monkey Ac-II: This animal received 32 units of insulin intramuscularly while in a fasting condition. Three and one-half hours after lapsing into coma it died and the brain was removed for study.

Grossly no pathologic changes were evident. Microscopically in the Nissl sections numerous Betz cells showed early swelling and beginning homogenization of the Nissl substance (fig. 5*A*). Many of the smaller cortical cells showed concentration of the Nissl substance at one side of the cell and numerous clearly abnormal vacuoles, which gave the cells a characteristic moth-eaten appearance (fig. 5*C* and *D*). No such cells were to be seen in the control brains. Some of the large cells of the caudate nucleus showed swelling and concentration of the Nissl substance at one side of the cell (fig. 5*B*). There was no clear evidence of pathologic changes in the ganglion cells of the cerebellum, cord or medulla or in the glia anywhere in the brain (Nissl and Hortega stains). There was swelling of capillary endothelial cells in some parts of the cortex (fig. 5*C*). Fat stains revealed nothing abnormal.

Monkey Ac-M: This animal received 160 units of insulin intramuscularly while in a nonfasting condition. Five and one-half hours later it was only slightly drowsy and was therefore given an additional 80 units; a half-hour later it lapsed into coma. The sugar content of venous blood at that time was 25 mg. per hundred cubic centimeters. Four hours after the onset of coma the animal became somewhat restless and began to respond to painful stimuli. It was therefore given an additional 50 units of insulin intramuscularly. One-half hour later it was killed by bleeding from the heart and the brain was removed for study. The sugar content of the blood (venous) just before death was 19.4 mg. per hundred cubic centimeters The total duration of coma was four and one-half hours.

Grossly no pathologic changes were observed. Microscopically the ganglion cells in various parts of the cortex (Nissl stain) showed swelling of the cell bodies and concentration of the Nissl substance in one half of the cell. The cytoplasm had a sandy appearance, which likewise gave the surface of the cells a beaded appearance, suggesting early incrustation. No such cells were seen in the control brain, and it was thought that they were abnormal. Ganglion cells in the basal ganglia, cerebellum, cord and medulla showed no clear pathologic change, nor was there any evidence in any part of the brain of changes in the blood vessels or glia elements (Nissl stain).

Monkey Ac-III: This animal received 16 units of insulin intramuscularly while in a fasting condition. It began to emerge from the ensuing coma three hours after the onset and was therefore given an additional 8 units of insulin intramuscularly. The second period of coma was terminated by the animal's death. The total duration of coma was nine and one-third hours.

Grossly the brain appeared congested. There was a blanched area, 2 mm. in extent, on the cut surface of the cortex of the left frontal lobe. Microscopically, one saw in the Nissl material numerous areas throughout the cortex where the ganglion cells had become mere shadows. In some cells the entire cytoplasm had

disappeared, so that only the nuclei remained (fig. 6 *A* to *E*). On studying these areas one gained the impression that there were fewer nerve cells here than in other relatively well preserved adjacent areas, as though a certain number of the nerve cells had disappeared entirely. Elsewhere in the cortex were many ganglion cells which were not so much swollen as moth eaten, owing to the vacuolation of their

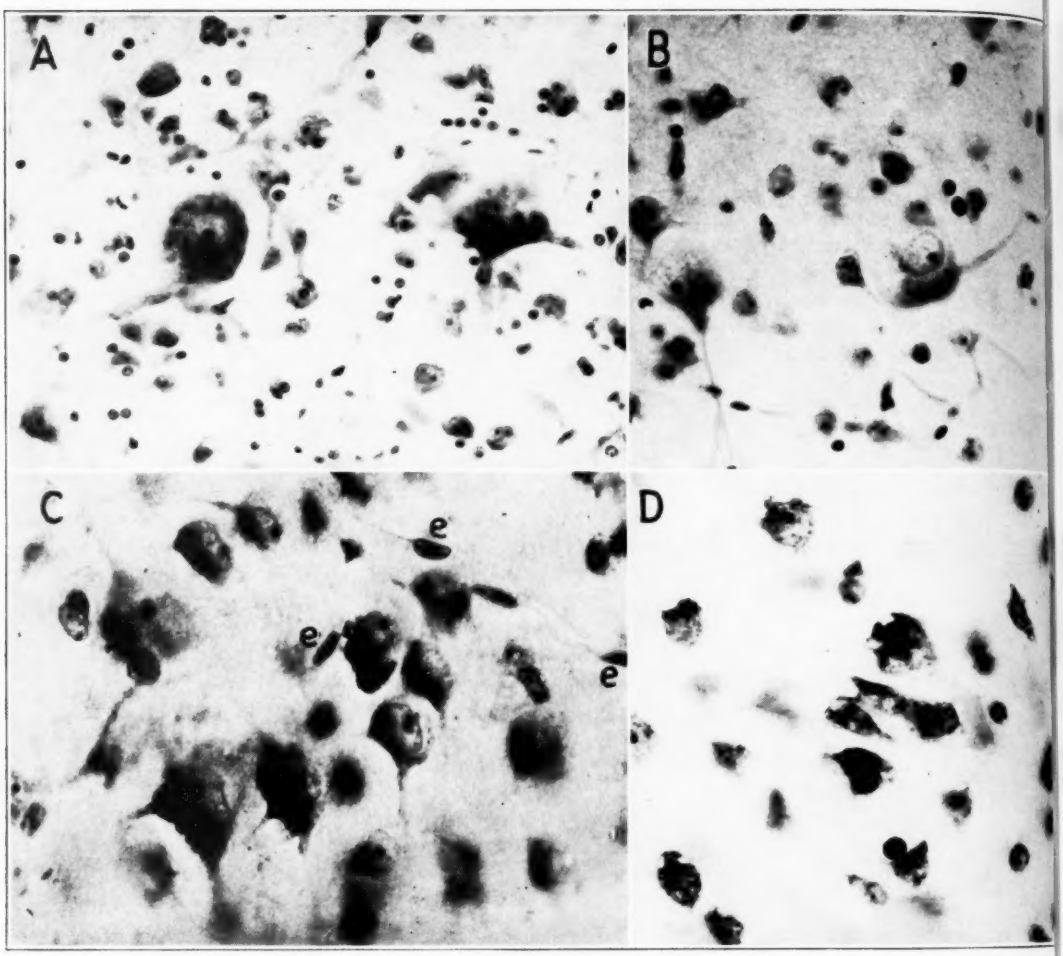

Fig. 5.—*A*, changes in the ganglion cells in an animal that died after a single hypoglycemic coma of three and a half hours' duration; swollen Betz cells of the motor cortex in which the Nissl bodies are fairly well preserved. × 290.

B, swelling and homogenization of the Nissl substance in two large nerve cells of the caudate nucleus. × 333. *C*, smaller nerve cells showing swelling and homogenization of the Nissl substance, which is concentrated in one portion of the cell. Notice swelling of endothelial cells (*e*). × 333. *D*, medium-sized pyramidal cells of the cortex showing vacuoles within the cytoplasm. × 290.

cytoplasm (similar to those shown in figure 5*D*). Cells in a small band in Sommer's sector presented the same moth-eaten appearance (fig. 7*C*); other cortical cells were shrunken, with pyknotic nuclei (fig. 6*F*). In parts of the cortex the axons showed early pigmentary degeneration, similar to that shown in figure 7*B*. No evidence of pathologic changes was seen in the nerve cells

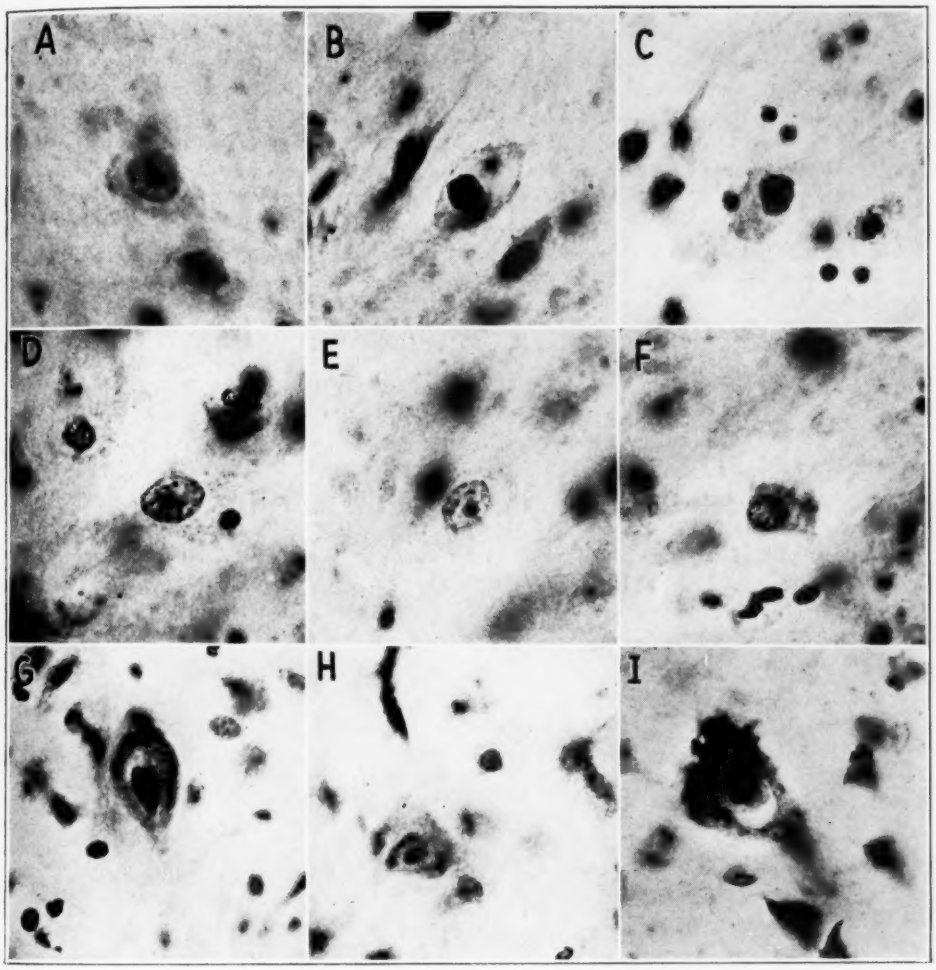

Fig. 6.—*A*, *B*, *C*, *D*, *E* and *F* illustrate acute nerve cell changes of a variety of types in an animal that had been kept in a single coma for nine and a third hours. *G* and *H* represent abnormal nerve cells from an animal that had a series of 40 insulin comas, and *I* shows an abnormal Betz cell, with breaking down and concentration of the Nissl substance at one end of the cell. The animal was killed at the end of a single insulin coma of twenty-two hours' duration. × 750.

elsewhere in the brain or in the glia in any part of the brain (Hortega stains for microglia and oligodendroglia and the Nissl stain). Fat stains revealed nothing abnormal.

Monkey Ac-IV: This animal received an initial dose of 16 units of insulin intramuscularly while in a fasting condition. It was kept in coma for fourteen hours before it died. Twice during this period it became restless and on each occasion was given 8 additional units of insulin intramuscularly. The brain was removed for study promptly after the animal's death.

Grossly the brain showed numerous areas of blanching of the cut surface of the cortex, especially in the section through the parieto-occipital region. Nissl stains showed acute swelling and vacuolation of the ganglion cells in many regions of the cortex. All layers were involved, but the superficial more than the deeper cortical layers. Swollen Betz cells with homogeneous Nissl substance were observed (fig. 8 *B*). One rather sharply circumscribed area was found in which most of the nerve cells had dropped out. In one portion of the frontal cortex the fourth layer stood out because of the marked swelling and vacuolation of its nerve cells. Occasional deeply stained and shrunken ganglion cells were seen. In stretches of the frontal cortex one saw marked decrease in the nerve cells of the second and third layers. The axons of the remaining nerve cells stained abnormally deeply (fig. 7 *B*) in this region. There was a distinct decrease in the number of nerve cells in Sommer's sector of the cornu ammonis. The remaining nerve cells were swollen, vacuolated and poorly stained. In the putamen there was swelling of the small nerve cells. The large cells of the globus pallidus showed homogeneous cytoplasm and a rounded contour. The changes in the glia were limited to the astrocytes, which with the Nissl stain showed swollen and abnormally vesicular nuclei in the involved cortical regions (fig. 7 *B*). The endothelial cells of many of the capillaries were swollen. Small and medium-sized cortical vessels in some regions of the frontal part of the brain were filled with white blood cell thrombi. The meninges of such zones frequently showed cellular infiltration (fig. 7 *A*).

Monkey Ac-A: This animal received 40 units of insulin intramuscularly while in a fasting condition. Four hours later it was found to be in deep coma and was given 11 Gm. of dextrose by stomach tube. Twenty-two hours later the animal was found to be still comatose; it died during attempts to administer more dextrose. The brain was removed promptly for study.

No observations on the gross appearance of the brain were recorded. Microscopically the changes were similar to those in the brain just described. The Betz cells were swollen, with homogeneous cytoplasm in some places, while in others they were deeply stained and shrunken, with incrustations and hyperchromic processes (fig. 8 *C*). The smaller ganglion cells throughout the cortex showed various stages of swelling and vacuolation, while in places there was well marked hyperchromic degeneration of the axons (similar to figure 7 *B*). Some Betz cells were surrounded by microglia nuclei and were presumably undergoing lysis (fig. 7 *D*). No clear evidence of pathologic change was seen in the ganglion cells of the basal ganglia, cerebellum, cord or medulla. In addition to the microglial reaction about dead or dying nerve cells already noted, there was evidence of reaction on the part of the astrocytes in the form of swollen, vesicular nuclei, which were particularly noticeable in various parts of the first cortical layer (Nissl stain). No indication of pathologic change was observed in the blood vessels in any part of the brain.

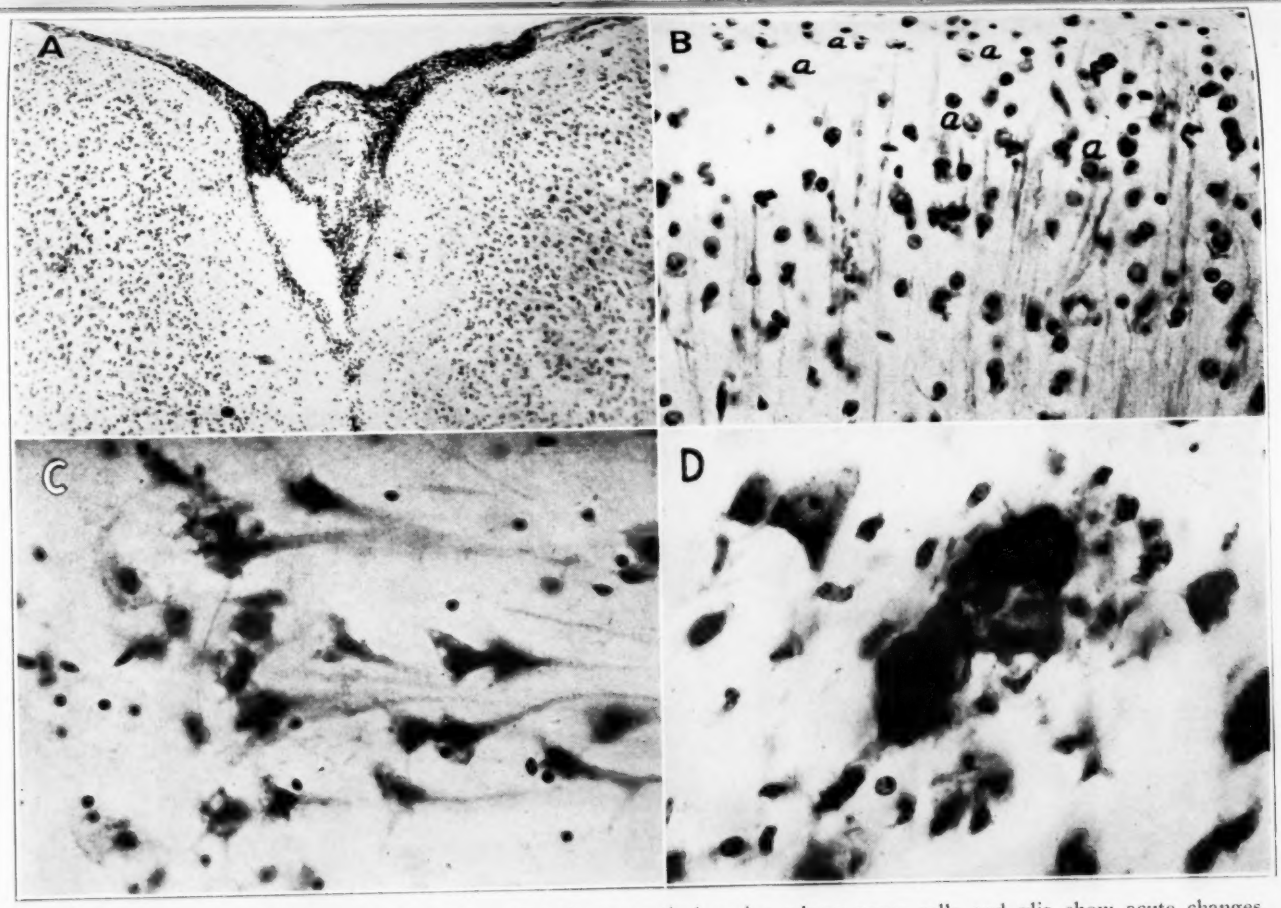

Fig. 7.—*A*, cellular infiltration of the meninges covering a cortical region where nerve cells and glia show acute changes. The animal was killed after a single insulin coma of fourteen hours' duration. × 60.

B, hyperchromatic staining of the axons in the cortex and numerous hyperplastic astrocytes (*a*) resulting from a single insulin coma of fourteen hours' duration. × 290.

C, vacuolated and moth-eaten appearance of nerve cells of the pyramidal layer of Sommer's sector in the cornu ammonis, resulting from a single insulin coma of nine and one-third hours' duration. × 290.

D, neuronaphagia of cortical nerve cells in the animal killed after a single coma of twenty-two hours' duration. × 630.

Summary and Comment on the Anatomic Changes in the Animals Which Had a Single Insulin Coma.—In the brains of 2 of the 3 animals which had been in coma for three and a half to four and a half hours, the essential changes noted were acute swelling and vacuolation of nerve cells (fig. 5). This is the type of ganglion cell change which is generally considered to be reversible. When the coma had lasted nine hours or more, however, many nerve cells were seen in which clearly irreversible changes had taken place (figs. 6 *A* to *E* and 7 *B* to *D*), including early pigmentary degeneration of the axons. In the brain of

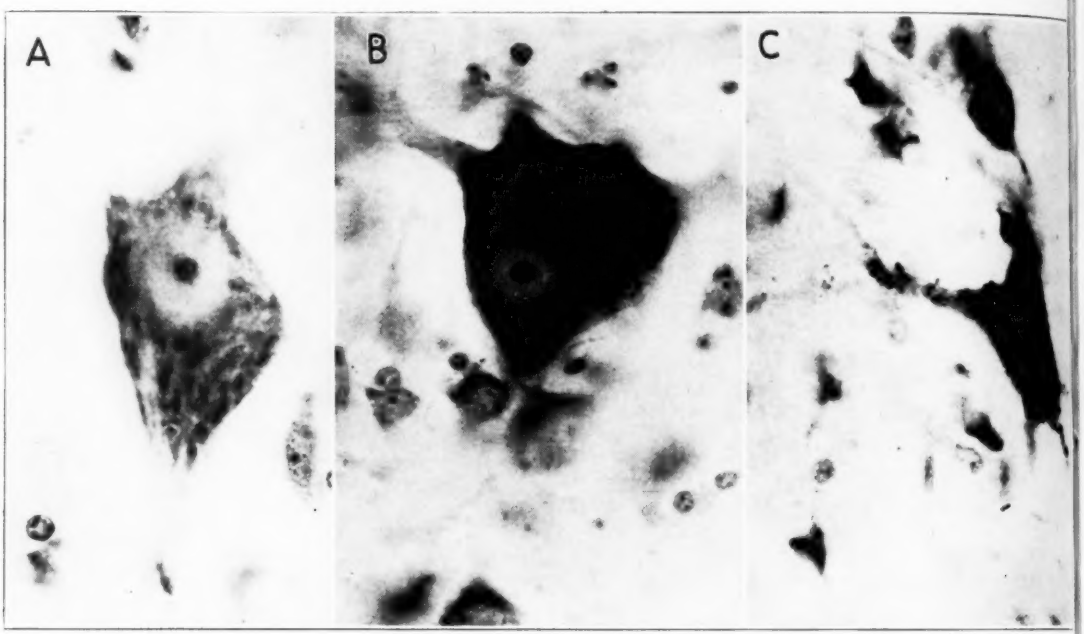

Fig. 8.—*A*, Betz cell in the motor cortex of a normal control mokney. × 650.

B, swollen Betz cell with homogenization of the cytoplasm resulting from a single insulin coma of fourteen hours. × 650.

C, shrunken deeply stained pyknotic Betz cell, with incrustations along the processes of the neuron, resulting from a single insulin coma of twenty-two hours. × 650.

the animal which had been in coma for fourteen hours there was extensive dropping out of nerve cells in various regions of the cortex and also in Sommer's sector. In general, the evidence of damage to nerve cells in all of these brains was much more clearly marked in the cortex than in the basal structures. When the coma had lasted fourteen hours evidence of glial reaction began to appear in the cortex, in the form of swelling of the astrocytes. Swelling of the capillary endothelial cells

was apparent also. In the cortex of the animal which had been in coma for twenty-two hours, the astrocytes were even more swollen and there was a vigorous microglial reaction.

We believe that these observations are of particular importance in view of the recent suggestions in the literature [5] that the duration of therapeutic insulin coma in psychotic patients be extended even up to ten hours. Our conclusion is that even a single such prolonged coma may cause extensive, irreparable damage to the brain. Moreover, coma of such duration might well carry a considerable risk of fatality, since de Morsier and Mozier [6] reported a case of accidental hypoglycemic shock in which dextrose was administered in large doses eight to nine hours after the onset of the coma without result, the patient dying two and one-half days later.

REPEATED INSULIN COMA EXPERIMENTS (TABLE 3)

Method.—This series consists likewise of 6 adult Macacus rhesus monkeys which received over a period of weeks a series of intramuscular injections of

TABLE 3.—*Data on Animals Subjected to Repeated Insulin Coma*

Animal	Number of Comas	Range of Duration of Coma, Hours	Average Duration of Coma, Hours	Duration of Experiment, Days
71*	9*	2¾-3¼	3	17
33	29	1¾-3	2¾	52
75	31	1¼-3	2¾	58
72	32	¼-4	2½	70
01	33	1½-3½	2¾	59
70	40	¼-4	2¾	87

* The animal died three hours after onset of the last coma; the brain was removed immediately. The remaining animals were killed.

insulin just sufficient to produce hypoglycemic shock for a desired period (table 3). With each animal we started with doses of insulin too small to produce shock, gradually increasing the dose until we reached the minimum number of units required to keep the animal in coma for a period of about two and a half to three hours. Unnecessary quantities of insulin were never given. In some instances, when the animal was found to be in too deep a coma, the amount of insulin was decreased in the subsequent injections. Each shock was terminated by the administration of 20 Gm. of dextrose in 50 per cent solution by stomach tube. The duration of the shortest coma was fifteen minutes and that of the longest four hours, with the average duration varying from two and a half to three hours for the 6 animals. The individual injections of insulin varied from 8 to 40 units, the average dose being about 20 units.

5. Kraulis, W.: Der protrahierte Schock in der Insulinbehandlung der Schizophrenie und Ergebnisse der Therapie in Riga-Lettland, Schweiz. Arch. f. Neurol. u. Psychiat. (supp.) **39**:219-221, 1937.

6. de Morsier, G., and Mozier, J. J.: Lésions cérébrales mortelles par hypoglycémie au cours d'un traitement insulinique chez un morphinomane, Ann. de méd. **39**:474-487 (May) 1936.

As noted in table 3, monkey 71 died three hours after the onset of the ninth coma. Its brain was promptly removed for study. All the other animals were killed after the termination of the experiments. In the latter half of the experimental period it was observed that monkey 70, though active, seemed clumsy and would frequently bump against the sides of the cage. This observation is extremely interesting in the light of the subsequent pathologic observations on the animal's brain.

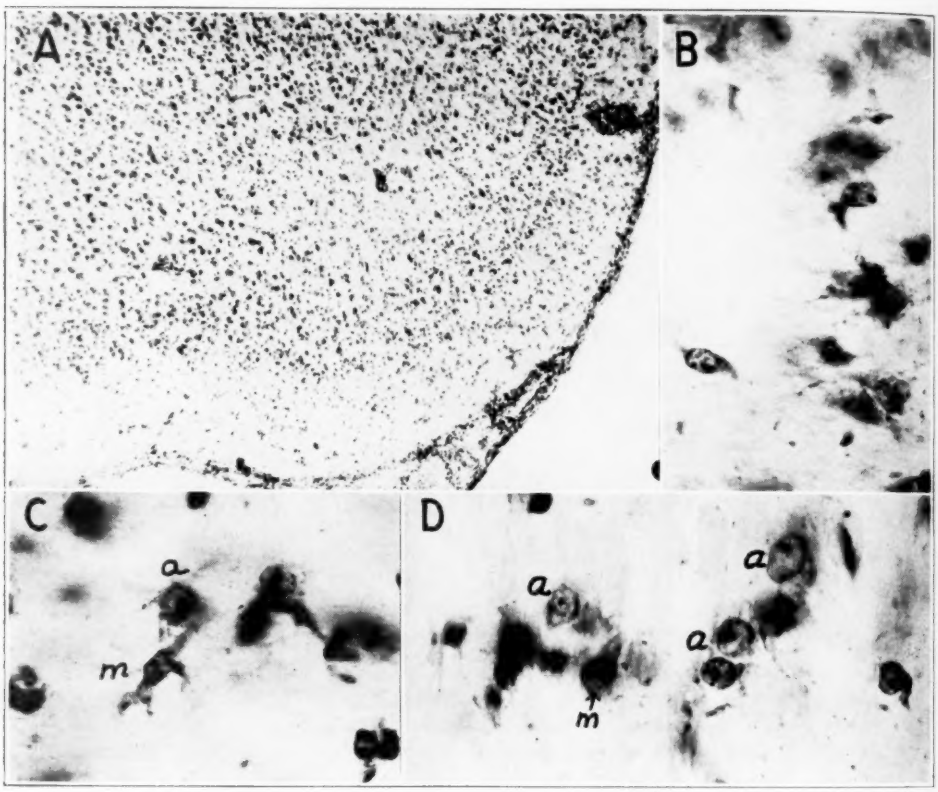

Fig. 9.—Changes in ganglion and glia cells in the monkey killed after the ninth insulin shock.

A, a region in the second and third layers of the cortex in which there is destruction of nerve cells. In addition, notice the proliferation of interstitial cells, particularly astrocytes and microgliocytes, in the first cortical layer, as well as in the region where the nerve cells are missing. × 60.

B, hypertrophic reacting astrocytes taken from the first cortical layer illustrated in *A*. × 630.

C, hypertrophic and reacting astrocytes (*a*) and a swollen microglia cell (*m*) from the lesion in the second and third layers illustrated in *A*. × 630.

D, proliferating and reacting astrocytes (*a*) and the mitotic figure of a microglia cell (*m*) from the first cortical layer of the lesion illustrated in *A*. × 630.

The brains of monkeys 33, 72, 01 and 70 were injected with india ink, fixed, sectioned and stained according to the technic already described in the general account of the metrazol experiments. The major portion of the brain tissue of monkeys 71 and 75 was fixed in 95 per cent alcohol and the remainder in dilute solution of formaldehyde U. S. P. (1:10). Sections (of 20 to 25 microns) from the alcohol-

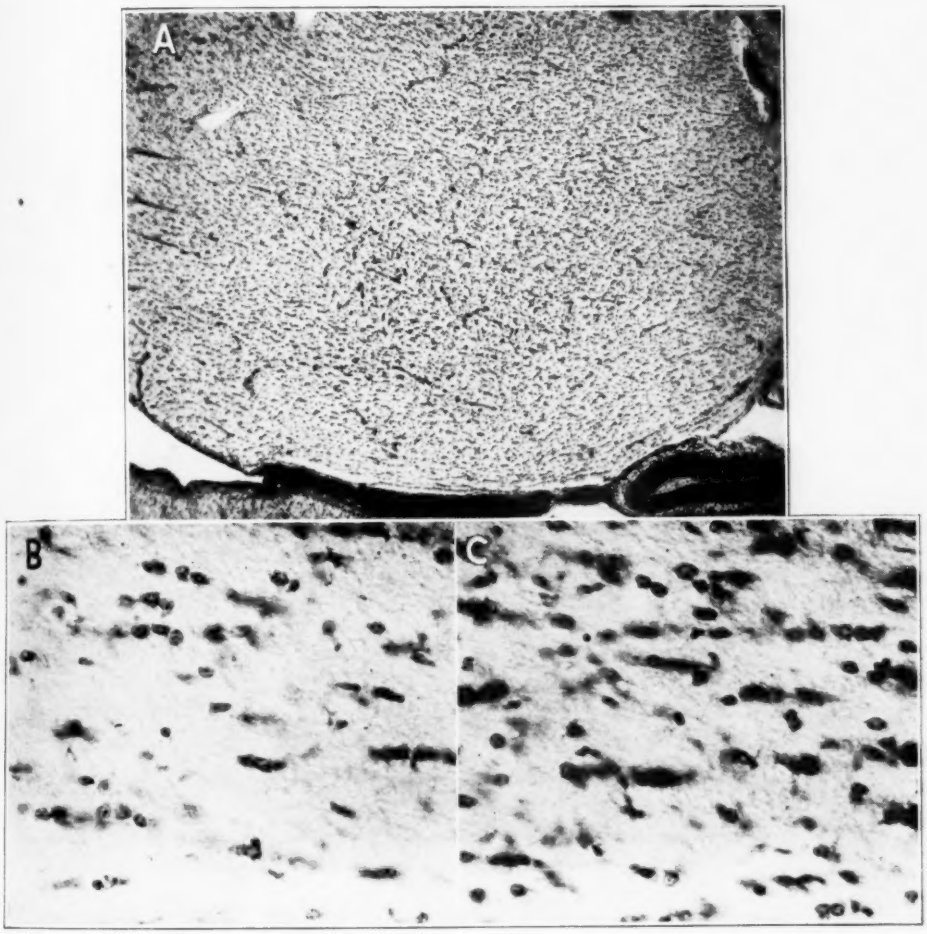

Fig. 10.—Oligodendroglial reaction in the optic tract of the animal killed after 9 insulin shocks.

A, acute reaction of the oligodendroglia in the center of the optic tract. × 30.

B, normal appearance and numbers of oligodendroglia cells taken from the periphery of the optic tract. × 320.

C, swelling and increase in the oligodendroglia cells in the center of the optic tract. × 320.

fixed material of each brain were stained with thionine. From the formaldehyde-fixed material of each brain sections were prepared by the following stains: scarlet red and alum hematoxylin for fat; the Cajal gold chloride method for astrocytes, and the Hortega silver carbonate method for microglia and oligodendroglia.

In none of the brains studied, either in the insulin or in the metrazol experiments, were serial sections of the entire brain examined. However, all of the brain tissue of each animal was saved and serial sections of a particular region could be, and in some instances were, prepared and examined. In fact, a very considerable proportion of each brain was actually subjected to microscopic scrutiny.

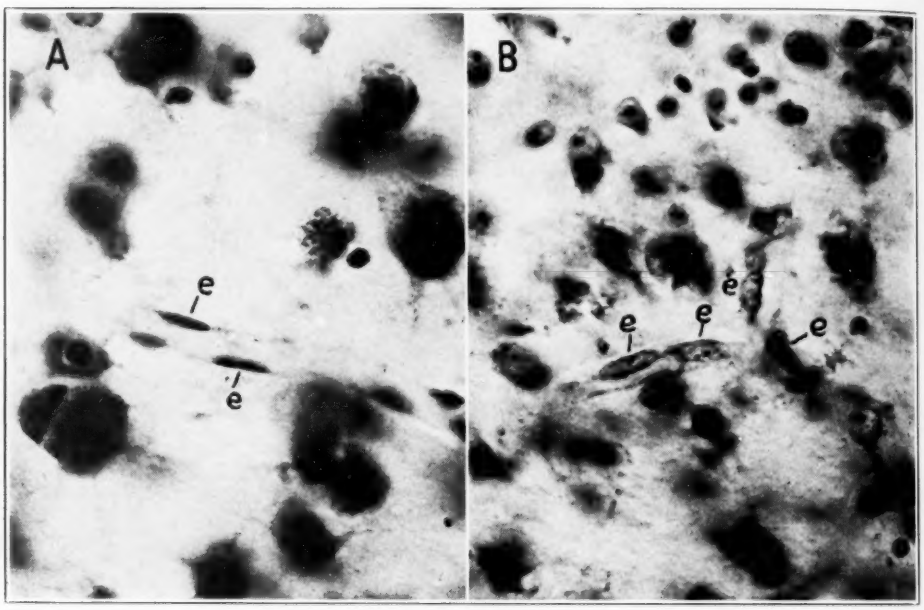

Fig. 11.—*A*, capillary showing the nuclei of normal endothelial cells (*e*) in the cortex of a normal control monkey. × 630.

B, swollen endothelial cells in the capillary from the area illustrated in figure 9 *A* from the animal which had received 9 insulin shocks. × 630.

Results.—Monkey 71: This animal was subjected to 9 hypoglycemic shocks in the usual manner. Three hours after the onset of the ninth coma the animal died. The brain was promptly removed for study.

Grossly the brain did not appear abnormal. Microscopically many parts of the brain showed evidence of severe damage. In several regions scattered throughout the neocortex the nerve cells were swollen and vacuolated and in various stages of disintegration up to complete disappearance, while around them the astrocytes and microglia cells were numerous and hypertrophic (fig. 9 *A* and *C*). This glial reaction was best observed in the first cortical layer, where it was not obscured by the presence of the dying nerve cells (fig. 9 *B* and *D*). These lesions seemed confined to the first three cortical layers, and their edges were not perfectly

sharp, but faded out gradually into the surrounding normal tissue. No pathologic changes in the ganglion cells were observed, except those in the cortex itself. A frontal Nissl section just posterior to the optic chiasm showed well marked proliferation of oligodendroglia in the heart of each optic tract (fig. 10 *A* and *C*). In the particular parts of the brain which were selectively stained for microglia no definite evidence of pathologic changes in microglia cells was observed. Within the zones of cortical destruction already described the endothelium of the capillaries could often be seen to be greatly swollen and to protrude into the capillary lumen (fig. 11 *B*).

Monkey 33: This animal was subjected to 29 hypoglycemic shocks in the course of forty-eight days. On the fourth day after the last shock the animal was given dial anesthesia and the brain injected with india ink.

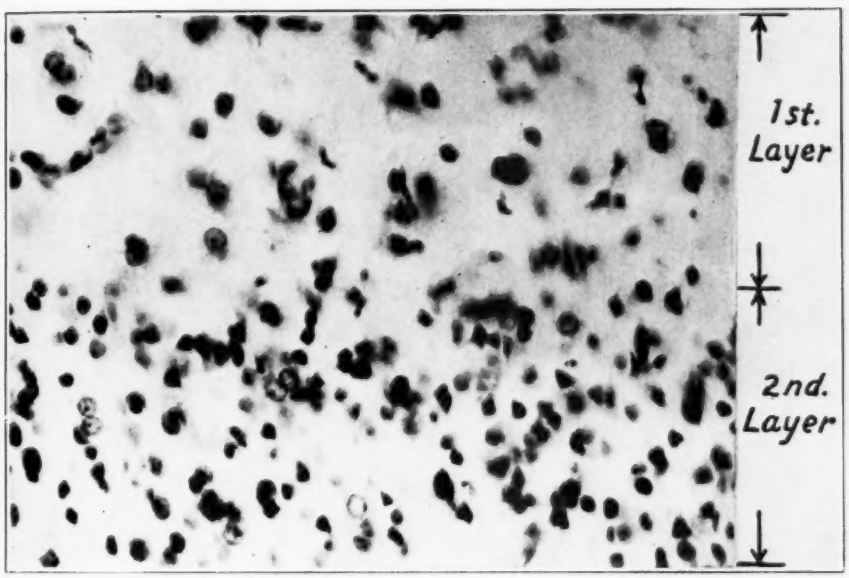

Fig. 12.—Swelling and hyperplasia of astrocytes in the first and second layers of the occipital cortex in the animal which had 31 insulin comas. The nerve cells in the second layer appear unchanged. × 350.

Grossly no pathologic changes were evident in the brain. Microscopically one saw numerous zones in the cortex, sometimes extending over several gyri, in which there were swelling and marked increase in the number of astrocytes, although the nerve cells in the same regions seemed essentially normal (similar to the picture in figure 12). An area in the fifth cortical layer was also observed from which nerve cells were absent. Here, again, there was evidence of active astrocytic proliferation. The cortical zones of glial reaction often extended down into the subcortical white matter. Here, proliferating microglia and astrocytes appeared to be present in about equal numbers. Foci of microglial reaction (similar to that shown in figure 18) were also observed in parts of the cerebral white matter far from the cortex, for example, in the corpus callosum. In the lateral geniculate bodies there were scattered areas, several millimeters square, in which no nerve cells

were to be seen. About the edges of these zones the nerve cells were swollen and incrusted, and in the zones themselves the oligodendroglia cells were swollen and more numerous and dark staining than normal.

Monkey 75: This animal received 31 hypoglycemic shocks in the course of fifty-five days. Three days thereafter the animal was killed and the brain removed for study.

Grossly no pathologic changes were evident in the brain. Microscopically in many areas in the cortex, particularly in the parieto-occipital region there were swelling and marked increase in the number of astrocytes, although the nerve cells in the same regions seemed essentially normal (fig. 12). In many other regions in the cortex the nerve cells were seen to be in various stages of disintegration. In these same regions there was tremendous proliferation of glia

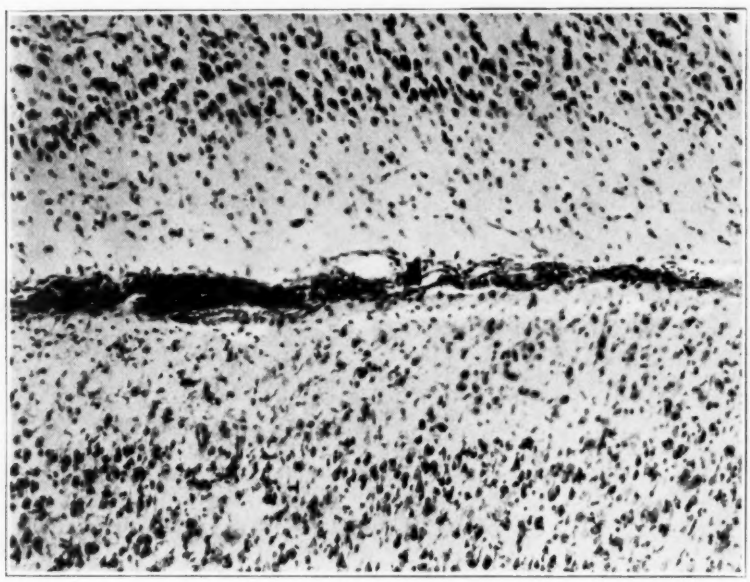

Fig. 13.—Adjacent convolutions, the upper normal and the lower convolution, illustrating an increase in astrocytes, which are hyperplastic. Notice the decrease in nerve cells in the second cortical layer of the lower convolution as compared with the corresponding layer of the upper convolution. The animal was killed after 31 comas. × 70.

cells, chiefly astrocytes with large nuclei and swollen, dark-staining cytoplasm, which often occurred in pairs or clumps (figs. 13 and 14 *B* and *D*). In addition, numerous mitotic figures were to be seen, indicating the presence of dividing microglia cells. The glial reaction was so pronounced as to cause these regions in Nissl preparations actually to appear more darkly stained than the other, normal parts of the cortex. Special glia stains confirmed the observations in the Nissl sections (figs. 15 *B* and 16 *C* and *D*). A similar region of damage to the nerve cells was seen in the cornu ammonis on one side, and here, in fact, the reactive gliosis was the most intense of any region in the brain (fig. 17 *B*). It should be noted that the edges of the cortical lesions were never sharp, and the swelling and proliferation of

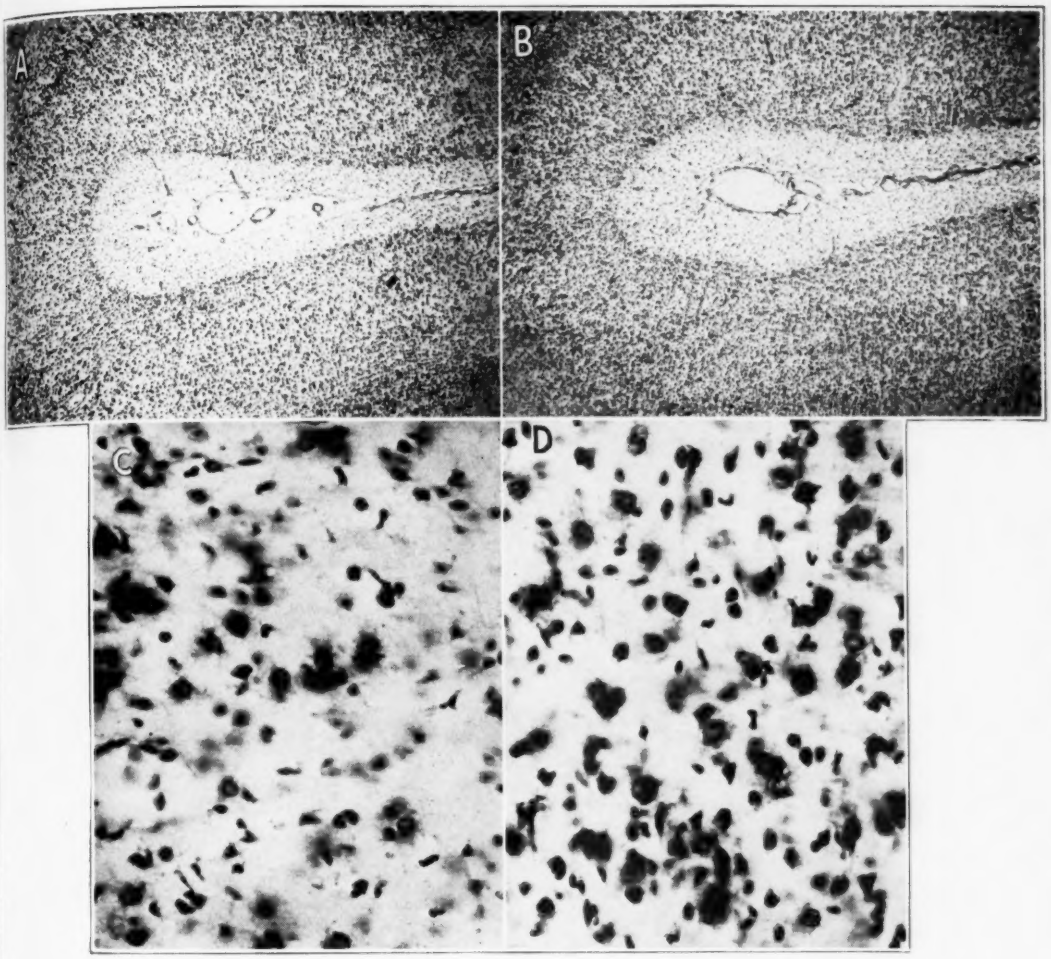

Fig. 14.—Proliferation of astrocytes and destruction of nerve cells in the cortex of the monkey killed after 31 insulin shocks.

A, normal cortex at the base of a convolution in the frontal lobe. × 24.

B, abnormal cortex at the base of a similar convolution from the opposite hemisphere. Note the definite increase in number of cellular elements, not only in the first layer but also in the deeper cortical layers, as compared with that in *A*. There is actually a decrease in the nerve cells of the deeper cortical layers, the apparent increase being due to the marked proliferation of astrocytes, as illustrated in *D*. × 24.

C, high power magnification of a section taken from the first cortical layer at the base of the convolution illustrated in *B*, showing marked increase in the astrocytes and their swollen vesicular nuclei and swollen cytoplasm. × 260.

D, the same reaction on the part of the astrocytes as that described in *C* in a section taken from the second cortical layer shown in *B*. Notice the absence of nerve cells, the increased cellular appearance being due to the proliferation and swelling of astrocytes. × 260.

glia cells extended out into the surrounding areas of the cortex, where the nerve cells were normal in number and appearance. The lesion in the cornu ammonis, however, was sharply outlined. In various parts of the white matter of the cerebral hemispheres, not only in the subcortex but also in the depths of the white matter and even in the corpus callosum, there were numerous foci of microglial reaction (fig. 18). There was no evidence of gitter cell formation, however, either in the Nissl sections or in the special fat preparations. Similar gliosis was apparent in the white matter of the cerebellar hemispheres (fig. 19). The vascular tree was not injected in this animal, but no special pathologic changes in the vessels were noted in the Nissl preparations.

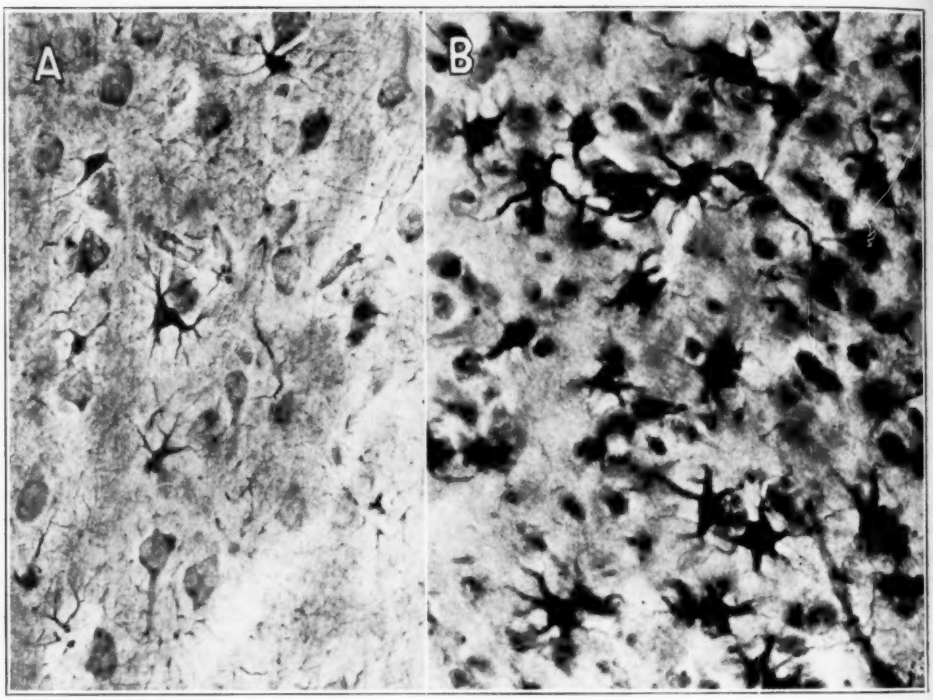

Fig. 15.—*A*, astrocytes in the cortex of a normal control monkey.

B, increase and hypertrophy of astrocytes in the cortex of the monkey which was killed after 31 insulin shocks.

Cajal gold chloride stain; 15 microns thick; × 760.

Monkey *72*: This animal received 32 hypoglycemic shocks in the course of sixty-nine days. On the day following the last shock it was anesthetized and the brain injected with india ink in the usual manner.

Grossly no pathologic changes were evident. Microscopically several regions in the cortex were observed in which the nerve cells were apparently well preserved, but in which there was active proliferation of the glia elements, chiefly astrocytes as far as could be determined in Nissl sections. Several other areas in the cortex showed massive falling out of nerve cells, usually in the superficial

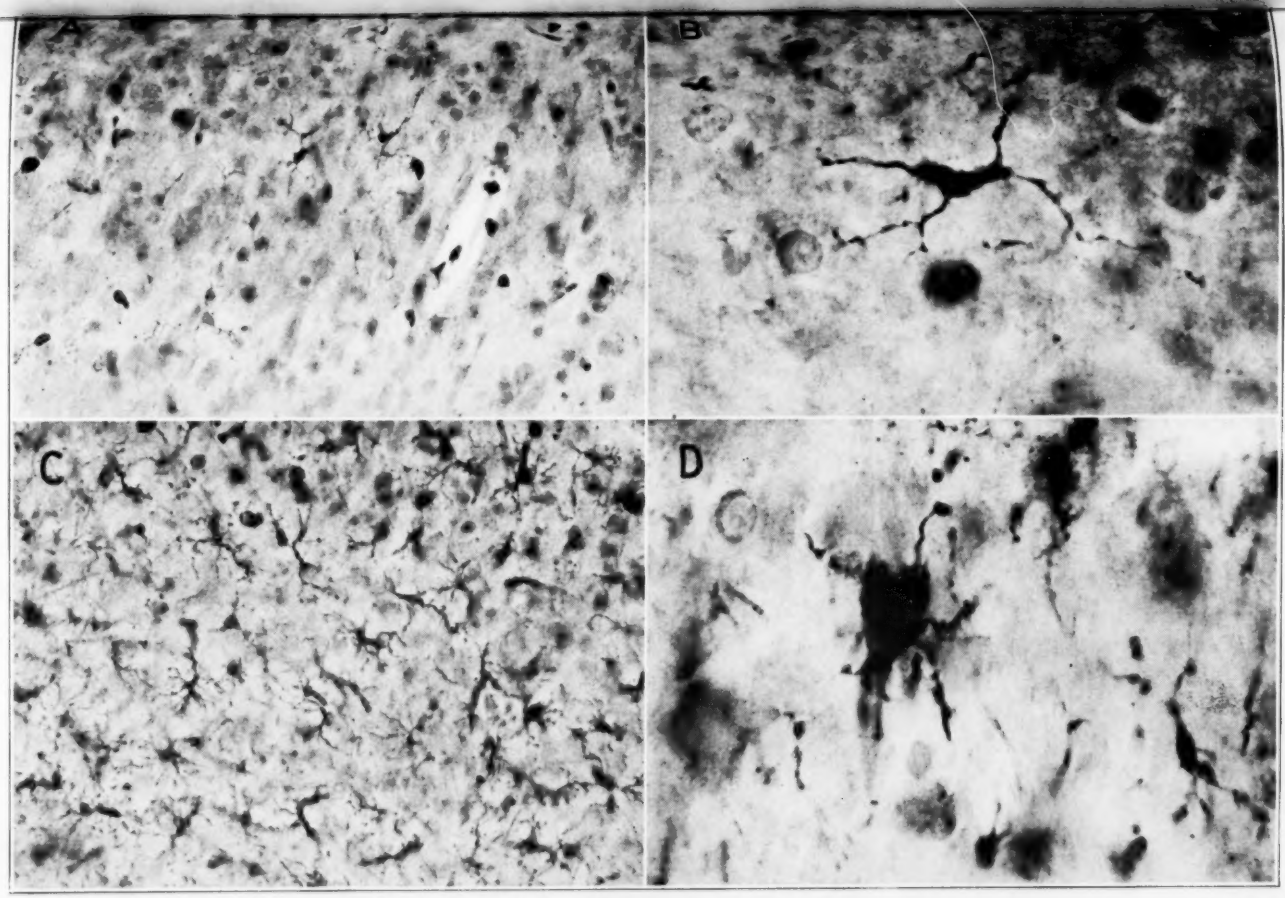

Fig. 16.—*A*, microglia in the cortex of a normal control monkey (15 microns thick; × 290).

B, high power magnification of the section shown in *A*. × 960.

C, large numbers of hypertrophic microglia in the cortex of the animal which was killed after 31 insulin shocks (15 microns thick; × 290).

D, high power magnification of the section shown in *C*. × 958. Hortega silver carbonate stain for microglia.

layers, producing pseudolamination (fig. 20 *D*). In such regions the glia elements were increased in number but were in a resting rather than an actively proliferating stage. In the cornu ammonis on both sides the nerve cells of Sommer's sector were entirely destroyed (fig. 21 *B* and *C*). In these areas there was a well marked subacute reaction of all three of the glia elements—microglia, astrocytes and oligodendroglia. As shown in figure 21 *E* and *F*, it was apparent in the thicker, unstained sections through the cornu ammonis that the capillaries in Sommer's sector bilaterally were thinner and fewer than normal. In the subcortical white matter there were foci of microglial reaction similar to those shown in figure 18. In addition, the microglia and oligodendroglia cells in the regions surrounding these foci appeared swollen and increased in number.

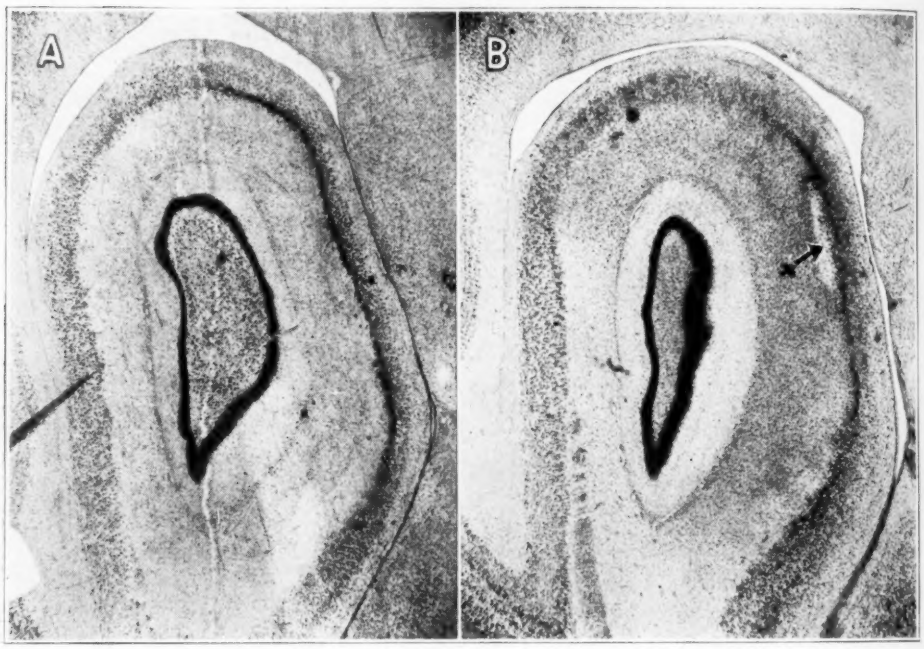

Fig. 17.—Glial reaction in the cornu ammonis of the monkey killed after the thirty-first insulin shock.

A, normal cornu ammonis in one hemisphere. × 12.5.

B, cornu ammonis from the opposite hemisphere. Note the increased density of cellular detail in the portion of the cornu ammonis facing the ventricle, which is due mostly to marked proliferation of astrocytes. This proliferation is also present in the area enclosed by the dentate fascia. The deep-staining band along the pyramidal layer is due entirely to proliferation of astrocytes, as the nerve cells have been destroyed. The relatively pale oblong area (marked *x*) is a circumscribed band of nerve fibers in which the proliferation of astrocytes has not occurred. × 12.5.

Monkey 01: This animal was subjected to 33 hypoglycemic shocks in the course of fifty-eight days. On the day following the last shock the animal was anesthetized with dial and its brain injected with india ink in the usual manner.

Grossly no pathologic changes were evident. Microscopically cortical lesions similar to those described in the brain of monkey 72 were seen. In some zones in the cortex the nerve cells showed evidence of damage and there was active

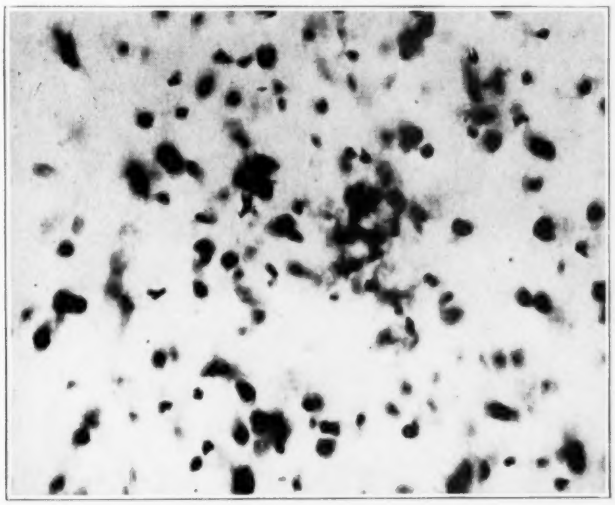

Fig. 18.—A nodule of proliferating and swollen microglia cells in the subcortical white matter of an animal which had received 31 insulin shocks. × 350.

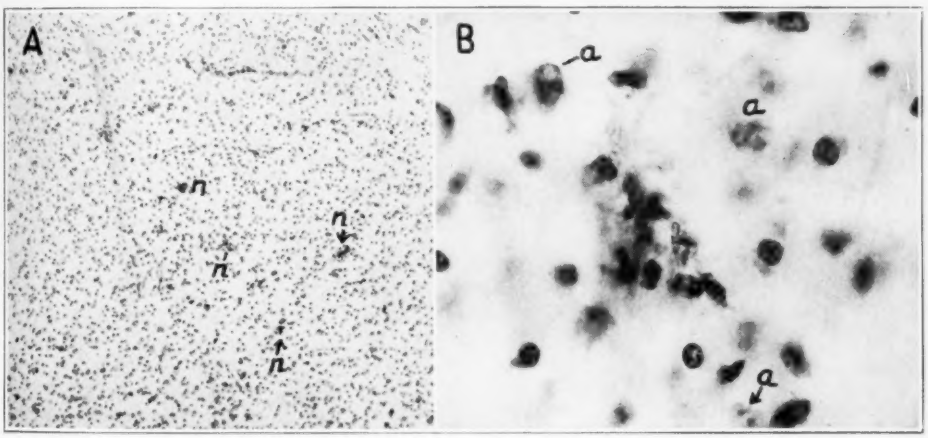

Fig. 19.—*A*, interstitial reaction in the cerebellar white matter in the animal which was killed after 31 insulin shocks. Throughout the illustration are increased numbers of pale-staining cells, which are astrocytes similar to those illustrated in *C* and *D* of figure 9. Note also the nodules of proliferating and swollen microglia (*n*). × 60.

B, high power magnification of one of the microglia nodules shown in *A*. Note also swollen astrocytes (*a*). × 650.

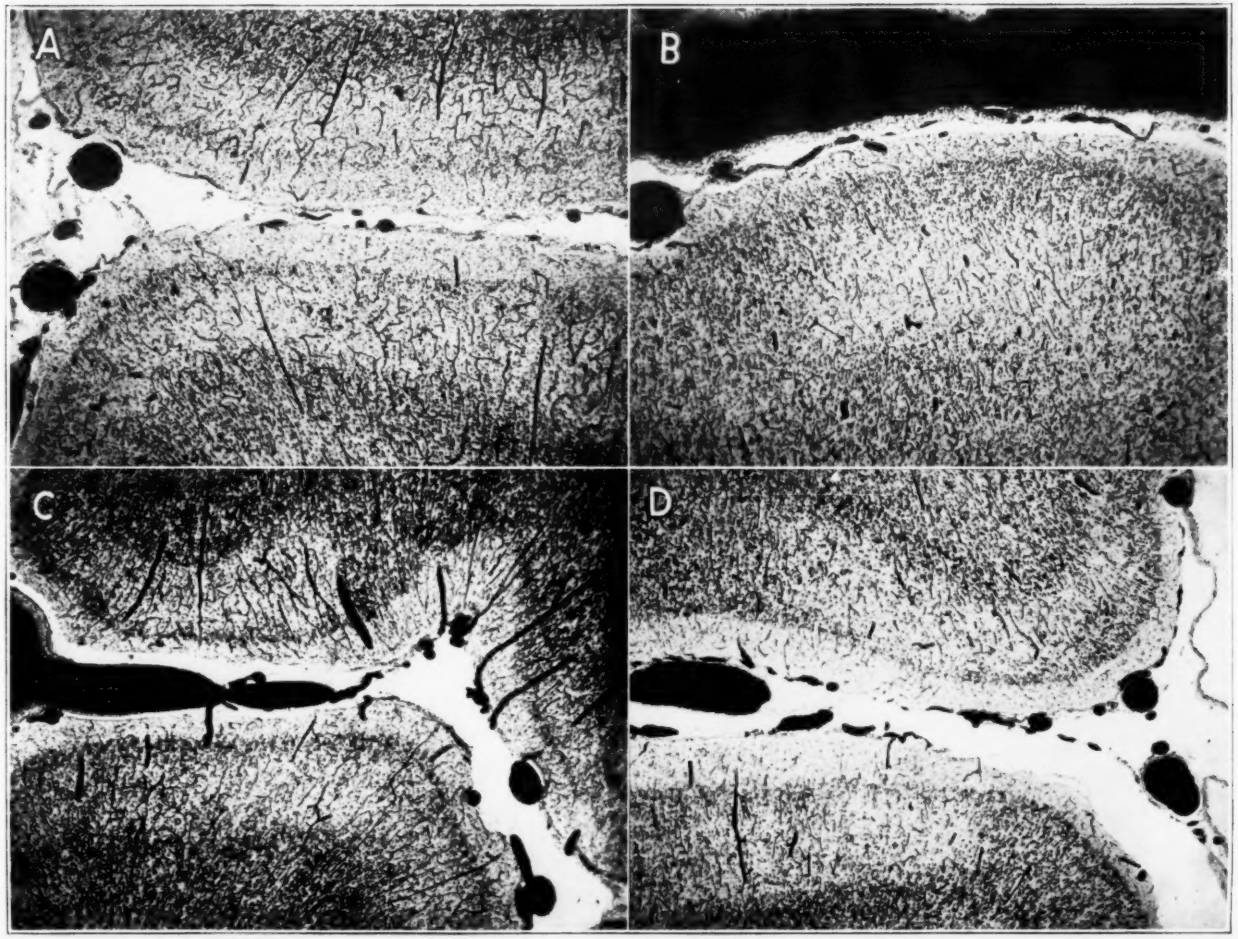

Fig. 20.—*A* and *B*, pseudolaminar falling out of nerve cells in the second and third layers of the monkey which had received 40 insulin shocks. × 27.5.

C, a similar picture in the animal which had received 33 shocks. × 27.5.

D, a similar reaction in the animal which was killed after 32 shocks. Note the tendency to symmetry in the pseudo-lamination in opposite quadrants shown in *A*, *C* and *D*. × 27.5.

C, a similar picture in the animal which had received 33 shocks. × 27.5.
D, a similar reaction in the animal which was killed after 32 shocks. Note the tendency to symmetry in the pseudo-
lamination in corresponding areas shown in *A*, *C* and *D*. × 27.5.

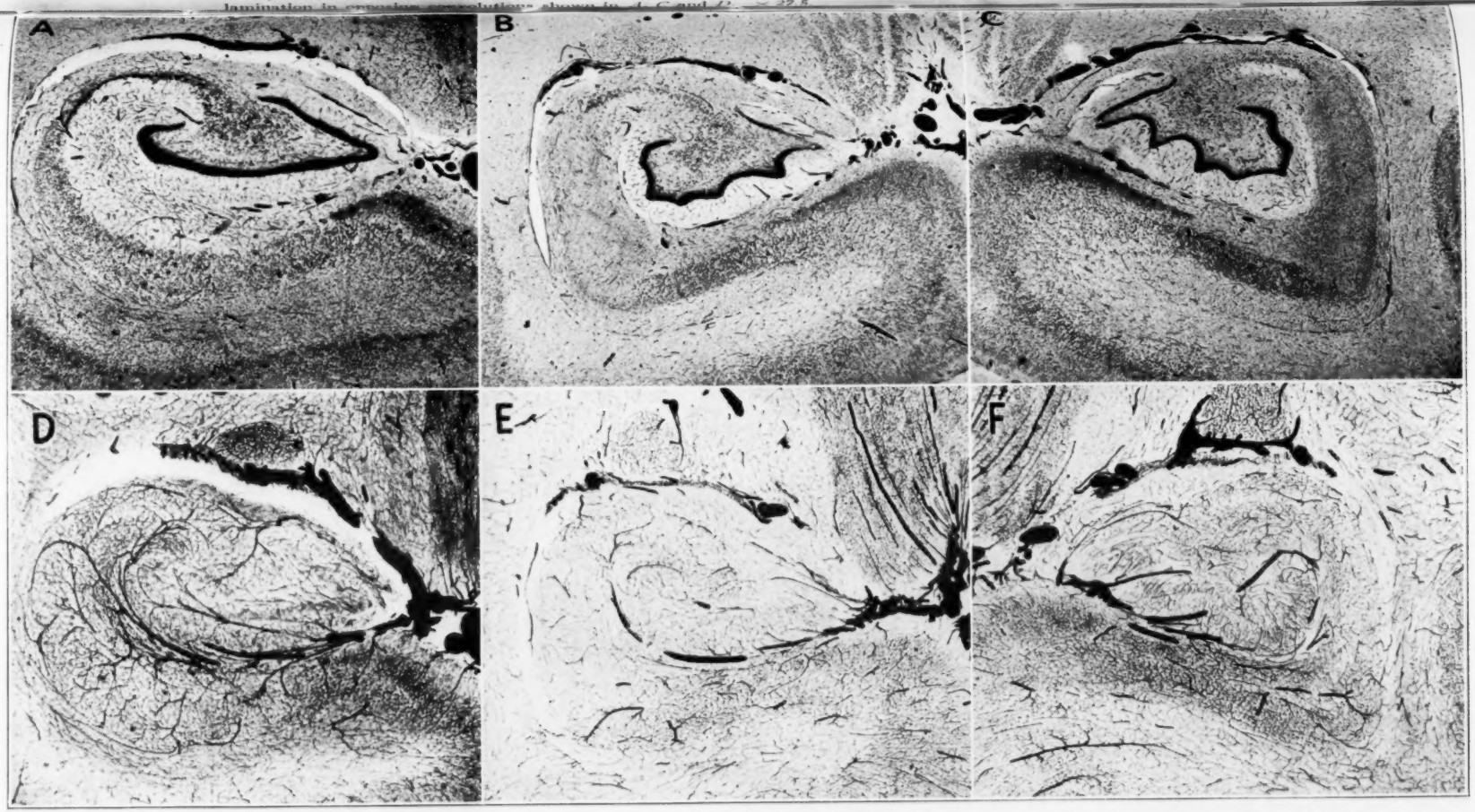

Fig. 21.—Cornu ammonis of a normal control brain as compared with the cornu ammonis of the two hemispheres from the animal killed after 32 insulin shocks.

A, cornu ammonis from a normal control monkey.

B and *C*, cornu ammonis of the left and the right hemisphere, respectively, of the monkey which was killed after 32 insulin comas. Notice the absence of nerve cells in Sommer's sector. Compare with *A*.

D, *E* and *F* are unstained serial sections adjacent to *A*, *B* and *C*, respectively, showing the capillary bed. *D* shows the normal vascular bed of the cornu ammonis, and *E* and *F*, the decrease in caliber and number of capillaries in Sommer's sector, corresponding to the region of nerve cell destruction in *B* and *C*. × 12.

proliferation of the glia elements, particularly the astrocytes (figs. 22 and 23). In other cortical regions (figs. 20 *C*, 22 and 24), there was massive falling out of nerve cells, particularly in the superficial layers, producing the picture of pseudolamination, while the glia cells, though increased in number, appeared to be in a resting rather than a proliferating stage. In some of the latter zones the capillary network was thinned, as clearly demonstrated in the lower gyrus in figure 20 *C*, whereas in others the capillary network appeared unchanged, as shown in a similar chronic cortical lesion in the upper gyrus in the same figure.

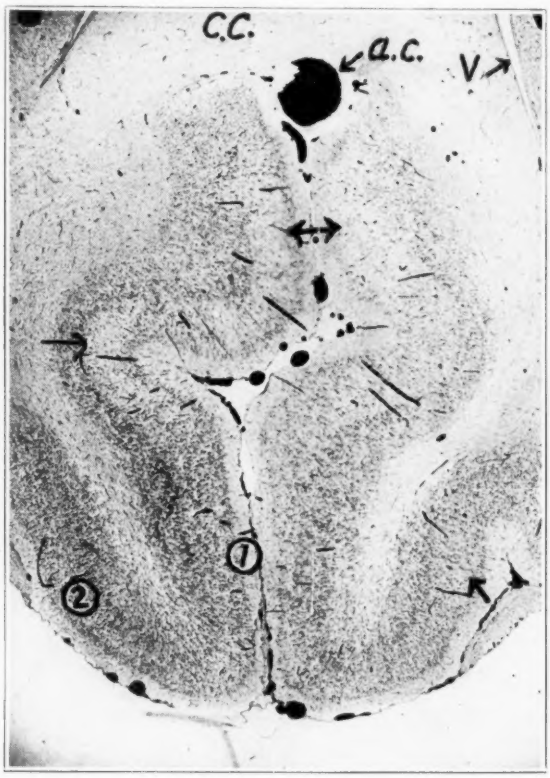

Fig. 22.—Pseudolaminar falling out of nerve cells (indicated by arrows) in the second and third, and to a less degree the fourth, cortical layers in the cortex. *c.c.* indicates the corpus callosum; *a.c.*, the anterior cerebral artery, and *v.*, the lateral ventricle. This section was taken from the animal which had received 33 insulin shocks. × 14.

Monkey 70: This animal received 40 hypoglycemic shocks in the course of eighty-six days. On the day following the last shock it was anesthetized and the brain injected with india ink in the usual manner.

Grossly no pathologic changes were observed. Microscopically a few cortical regions were seen in which there was evidence of active glial proliferation.

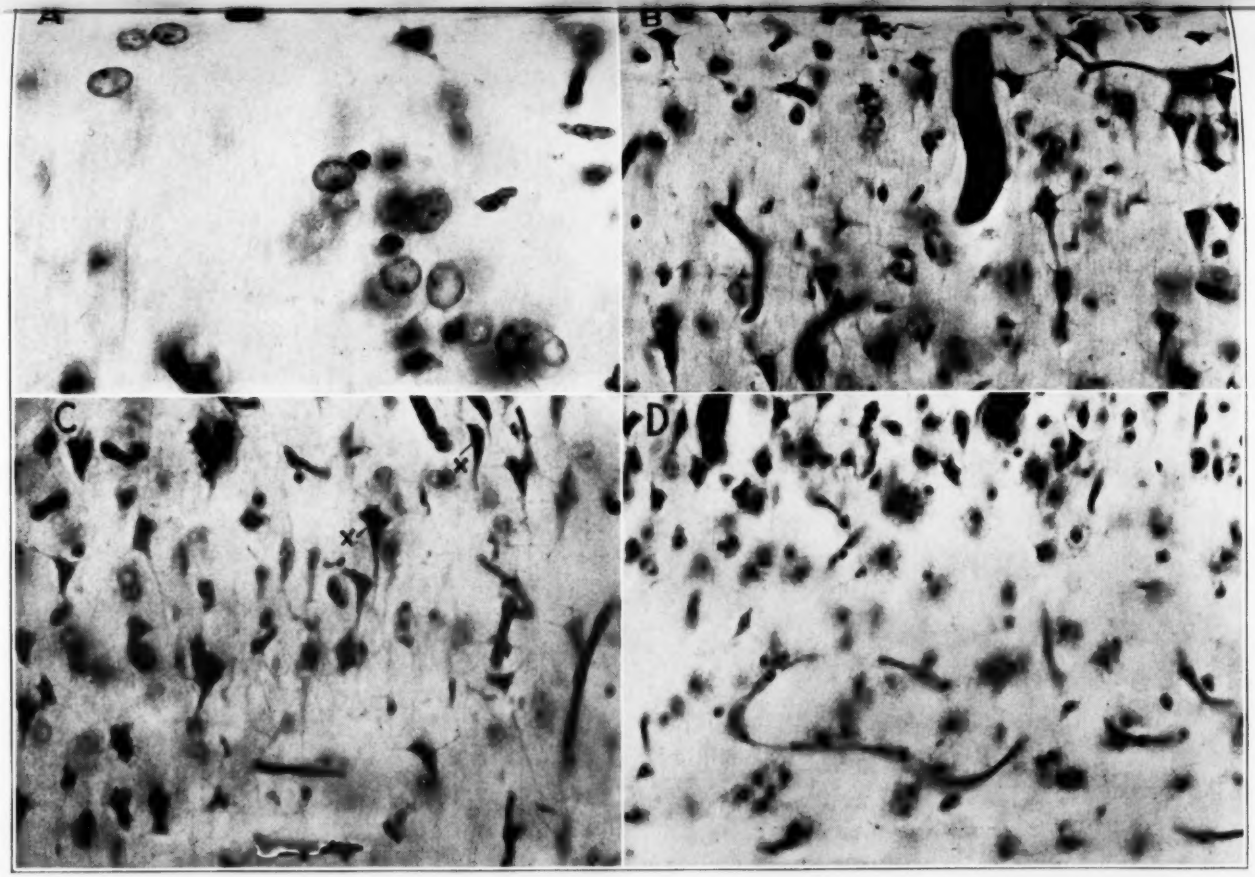

Fig. 23.—High power photomicrographs to illustrate the glial reaction in the cortical lesions shown in figure 22.

A, proliferation and swelling of astrocytes in the first cortical layer from circle *1*, figure 22. × 633.

B, swollen astrocytes in the second cortical layer near circle *1*. × 260.

C, proliferation and swelling of astrocytes from the third cortical layer (circle *2*), in which the nerve cells are still present, although some of them (*x*) appear shrunken and pyknotic. × 258.

D, an unusual type of hypertrophic astrocytic reaction from the first cortical layer of the cortex in the lateral part of the section from which figure 22 was taken. The nuclei of these astrocytes are smaller and darker and the cytoplasm stains deeper than those already illustrated. They may be older cells. × 258.

chiefly astrocytes (fig. 25 *A*, *C* and *D*), but in the majority of the cortical lesions the nerve cells of the superficial layers had completely disappeared and the glia cells were not actively proliferating (figs. 20 *A* and *B* and 25 *B*). Both lateral geniculate bodies contained almost no nerve cells, and there was a marked increase in the number of oligodendroglia cells (fig. 26 *B* and *D*). Consequently, this animal must have been blind, which accounts for the clumsy manner in which it bumped against the sides of the cage. Throughout the white matter of the cerebral hemispheres, including the corpus callosum, there were widespread swelling and evidence of proliferation of the glia cells, similar to the condition shown in figure 18. As is evident in figure 26, the capillaries in the lateral geniculate bodies were small in caliber and diminished in number.

Summary and Comment on Anatomic Changes in Monkeys Subjected to Repeated Insulin Coma.—Severe and extensive lesions were

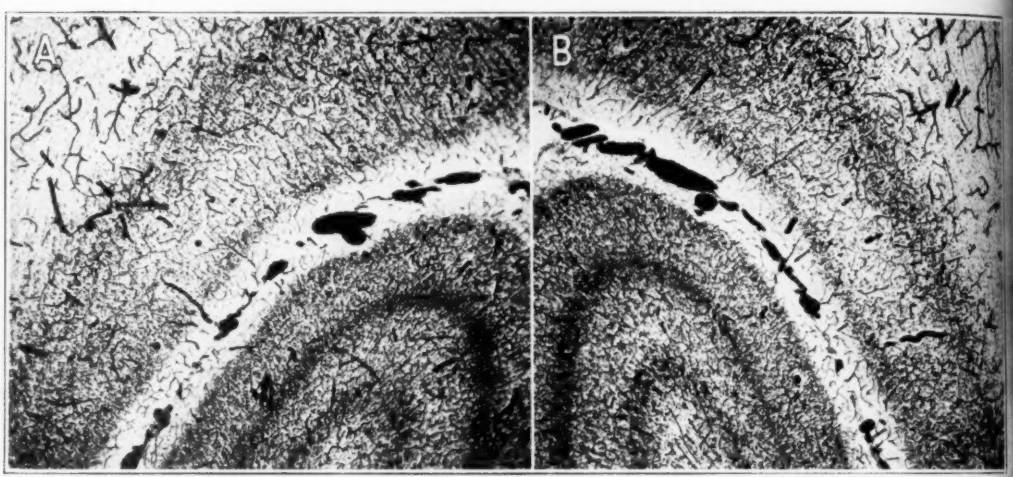

Fig. 24.—Pseudolaminar falling out of nerve cells in the second, third and fourth layers of the cortex in identical regions of the two occipital lobes. The exact symmetry of the pseudolaminar lesions in corresponding regions of the two hemispheres was in many instances remarkable. × 28.

found in the cortex of all the animals (figs. 9, 14, 20, 23 and 25) and in the cornu ammonis in 2 of them (figs. 17 and 21). The nerve cells in the lateral geniculate bodies were obliterated (fig. 26) in 1 animal and moderately damaged in another. On the basis of the observations described, we feel that we can postulate the following course of development of these lesions.

In the earliest stage there are proliferation and hyperplasia of the astrocytes, without any detectable histologic changes in the nerve cells themselves (fig. 12). As the damage becomes more severe the glial reaction becomes much more intense (figs. 15, 16, 17 and 23) and the

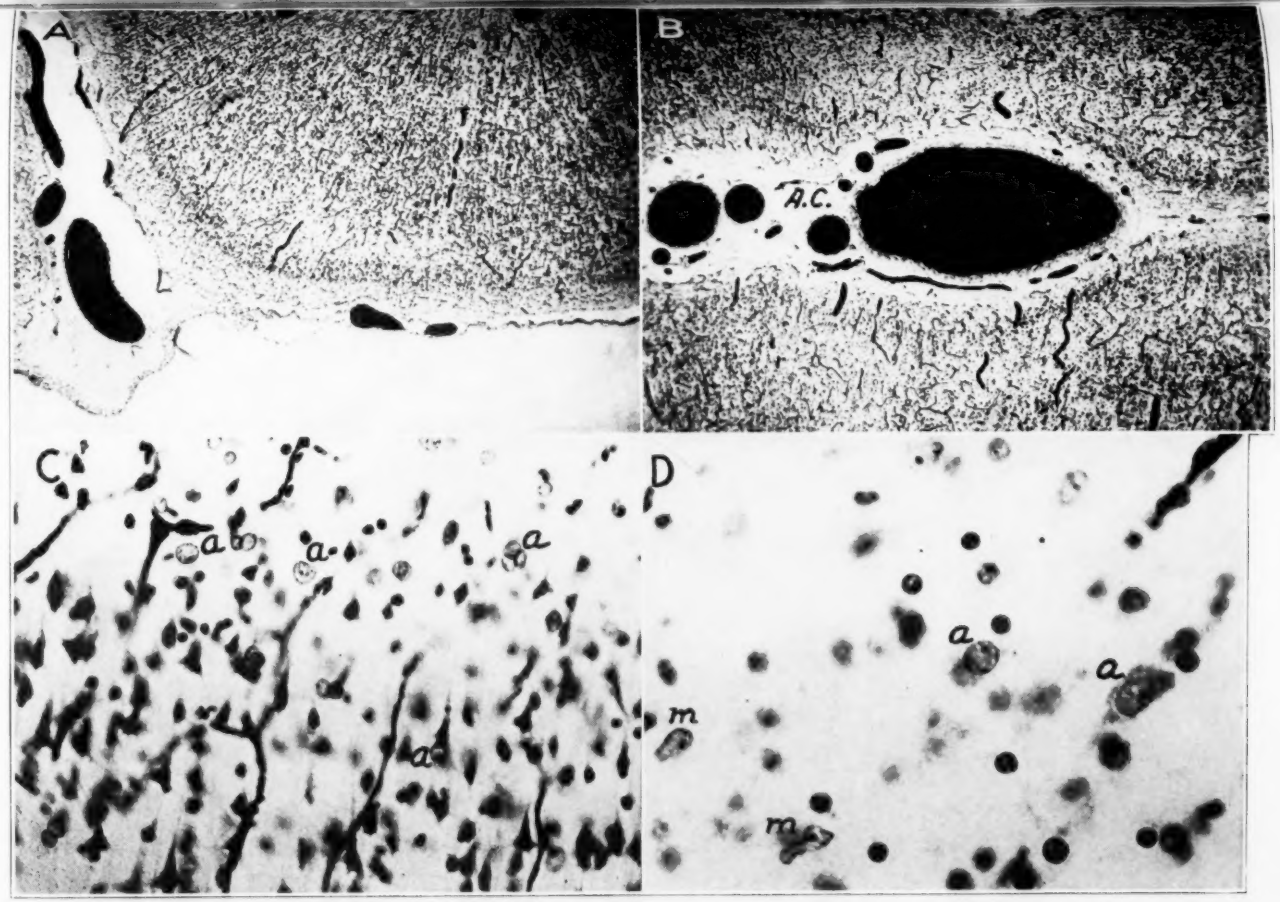

Fig. 25.—Pseudolaminar cortical lesions in the monkey killed after 40 insulin shocks.

A and *B*, pseudolaminar falling out of nerve cells in the second and third cortical layers. Notice the symmetry of the lesions in opposing gyri in section *B*, on either side of the anterior cerebral artery (*A.C.*). × 30.

C, proliferating and swollen nuclei of astrocytes (*a*) in the first and second cortical layers from *A*. × 320.

D, swollen nuclei of hypertrophic astrocytes (*a*) and microglia cells (*m*) from the subcortical white matter shown in *A*. × 690.

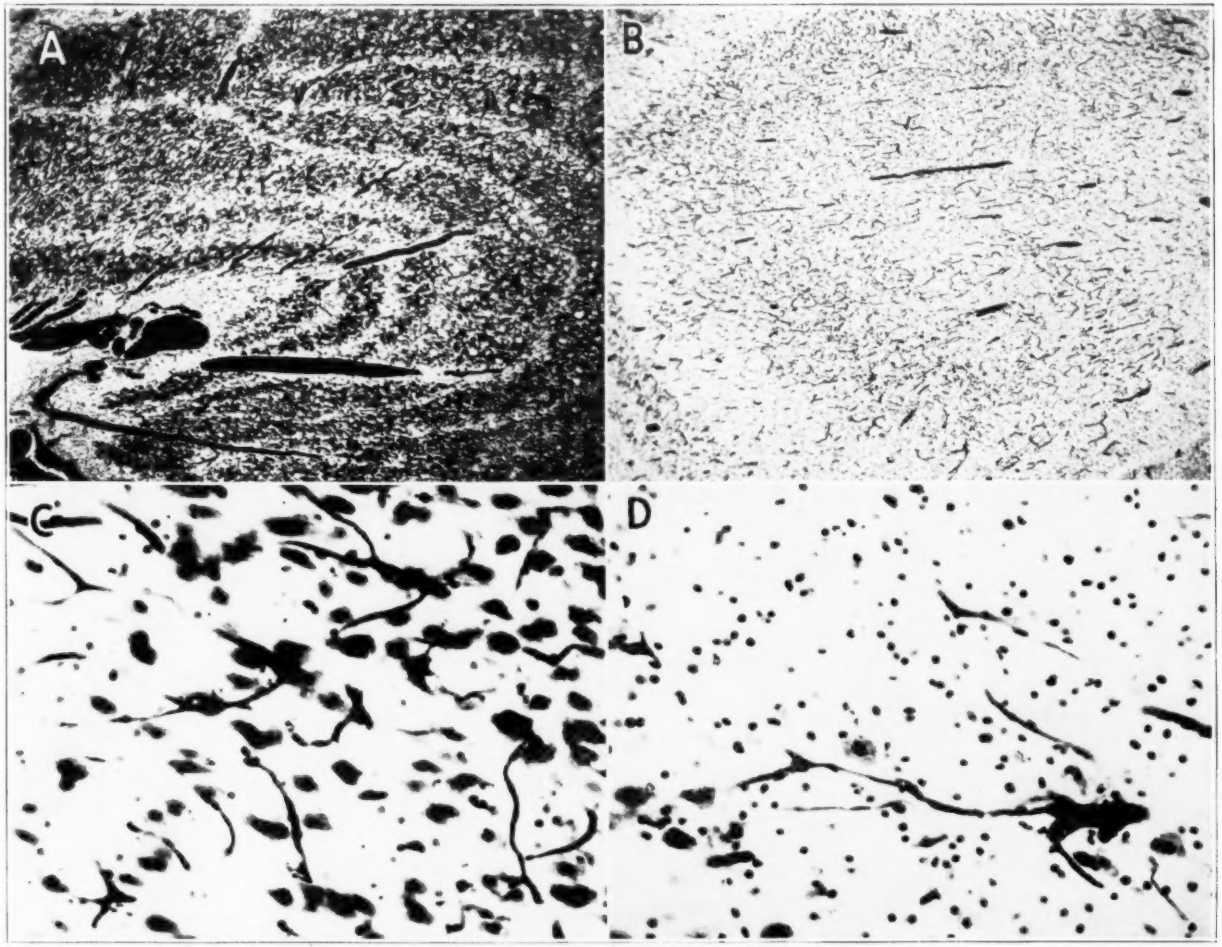

Fig. 26.—*A*, the external geniculate body from a normal control animal. × 27.5.

B, the external geniculate body from a monkey that was killed after 40 insulin comas. Notice the almost complete wiping out of the nerve cells. × 27.5.

C, high power magnification of the normal external geniculate body. × 260.

D, high power magnification of the abnormal external geniculate body. Notice the almost complete absence of nerve

nerve cells show evidence of chronic irreversible damage (figs. 13, 9, 14 and 23). Still more severe damage is represented by complete disappearance of the nerve cells from the involved area, leaving only glia cells, which are seen to be hypertrophic and increased in number (figs. 17 and 25). Finally the glia elements themselves return to a resting phase and only a zone devoid of nerve cells, often with pseudolamination, is to be seen (figs. 20, 21 and 26). Such acellular areas in the cortex were most frequently found in the upper cortical layers (fig. 20). What the significance of this apparent predilection may be we are not prepared to say. The pathogenesis of these lesions could be most clearly traced in the cortex, where lesions of all degrees of severity were observed. In the lateral geniculate bodies the only lesions seen had already reached the final stage of complete absence of nerve cells with resting glia (fig. 26). In the case of the cornu ammonis we observed lesions in the intermediate (fig. 17) and final (fig. 21) stages.

The type of glial response varied somewhat, depending on the location of the lesion. In the cortex the chief response was on the part of the astrocytes (figs. 9, 14, 15 and 23). However, mitotic figures could also be seen, indicating the presence of proliferating microglia (fig. 9 *D*), and silver stains showed the presence of increased numbers of hypertrophic microglia (fig. 16). No gitter cells were ever observed. In the lesions in the cornu ammonis all three types of glia cells appeared to have responded, although the astrocytic response predominated (fig. 17), while in the case of the lateral geniculate bodies the glial response was almost entirely limited to the oligodendroglia (fig. 26).

Another interesting observation was that in the case of cortical lesions in the intermediate stage the glial reaction extended well out into the surrounding areas of histologically normal nerve cells, so that the lesions had no sharply defined edges (figs. 22 and 23). In the cornu ammonis, however, the edge of the lesion in this phase was sharply demarcated.

Two types of vascular abnormalities were seen in conjunction with these lesions of the gray matter. In the early stages of acute glial reaction the capillary endothelium was sometimes observed to be swollen (fig. 11). In the injected preparation, however, we saw no essential alteration of the vascular bed in the region of the early lesions. In the more severe lesions (final stage), on the other hand, there were frequently diminution in caliber and decrease in number of the capillaries (figs. 21 and 26). We interpret this change as a response to a decreased demand of the tissue for blood supply following the neuronal destruction.

The white matter also showed widespread and striking pathologic changes not only in the cerebrum, both subcortical (fig. 18) and deep,

wiping out of the nerve cells. × 27.5.
C, high power magnification of the normal external geniculate body. × 260.
D, high power magnification of the abnormal external geniculate body. Notice the almost complete absence of nerve

but also in the cerebellum (fig. 19) and the optic tracts (fig. 10). The lesions in all parts of the white matter were characterized by absence of free fat. No gitter cells were to be seen. Stains for myelin sheaths and axis-cylinders were not made; consequently, only the glial reaction could be adequately determined. In the subcortical lesions, which were simply extensions of those in the overlying cortex, the glial reaction was essentially the same in the white as in the gray matter. Elsewhere in the white matter in the cerebral hemispheres and in the cerebellum the characteristic findings were foci of microglia (figs. 18 and 19) and a diffuse reaction involving all three types of glia cells about equally. In the optic tracts the reaction was confined essentially to the oligodendroglia (fig. 10).

We believe that all the histologic changes in the brains of this group of animals are thoroughly consistent with the view that the lesions observed represent the cumulative result of minor damage to the brain incident to each of the hypoglycemic shocks rather than that any one lesion was caused by a single shock. The apparently gradually progressive nature of the lesions of the gray matter is of course the strongest evidence in favor of such a point of view.

As far as we have been able to learn from the literature, previous experiments on the effects of insulin on the central nervous system have all been with quadripeds, chiefly rabbits or dogs. There is general agreement that in such experiments severe damage to nerve cells is produced. Stief and Tokay [7] reported involvement particularly of the cortex and the cornu ammonis, the nerve cells having completely disappeared from large areas of the cortex. Grayzel [8] also observed such areas, and Weil and his associates [9] reported diminution in the number of neurons in various cortical areas. None of these authors has particularly stressed the glial reaction, though Grayzel noted such a response in the areas where ganglion cells had dropped out and Stief and Tokay stated that it was present in some animals.

There are numerous clinicopathologic reports of cases in which the patients died as a result of accidental or therapeutically induced hypoglycemia. The pathologic changes appear to have been variable. In some cases there were gross cerebral hemorrhages or thromboses

7. Stief, S., and Tokay, L.: Beitrag zur Histopathologie der experimentellen Insulinvergiftung, Ztschr. f. d. ges. Neurol. u. Psychiat. **139**:434-461, 1932; Weitere experimentelle Untersuchungen über die cerebrale Wirkung des Insulins, ibid. **153**: 561-572, 1935.

8. Grayzel, D. M.: Changes in the Central Nervous System from Convulsions Due to Hyperinsulinism, Arch. Int. Med. **54**:694-701 (Nov.) 1934.

9. Weil, A.; Liebert, E., and Heilbrunn, G.: Histopathologic Changes in the Brain in Experimental Hyperinsulinism, Arch. Neurol. & Psychiat. **39**:467-481 (March) 1938.

(Baker,[10] Döring [11] and Kastein [12]). In others these vascular lesions were microscopic (de Morsier and Mozier [6]). Large areas, similar to those produced experimentally, from which nerve cells had entirely disappeared have been frequently described, and Leppien and Peters [13] and Cammermeyer [14] observed well marked pseudolamination. These authors also noted progressive glial changes in conjunction with damage to the nerve cells.

In most of the cases cited in these reports the patients died after a prolonged coma of eighteen hours or longer. In these instances the pathologic changes resulting from the prolonged terminal coma may have obliterated the changes due to the cumulative effects of the previous therapeutic periods of coma.

SUMMARY AND CONCLUSIONS

Four adult Macacus rhesus monkeys were subjected to a series of metrazol convulsions (15, 21, 45 and 48, respectively) during a period of several weeks. Microscopic examination of the brains of these animals showed two types of lesions: (*a*) small foci in the cortex in which nerve cells were missing and in some of which there was evidence of vascular damage, and (*b*) mild proliferation of astrocytes and hypertrophic changes in the microglia in scattered regions of the cortex.

The brains of 6 other Macacus rhesus monkeys were studied after the animals had been subjected to single insulin comas of varying durations (three and one-half, three and one-half, four and one-half, nine and one-third, fourteen and twenty-two hours, respectively). In the brains of the animals subjected to coma for three and one-half and four and one-half hours, respectively, there was acute damage to the nerve cells, probably of a reversible type. In the animals with coma for nine and a third hours severe damage to the nerve cells of the cortex of an irreversible character resulted. In the brains of the animals with prolonged coma of fourteen and twenty-two hours' duration, respectively, in addition to severe damage to the nerve cells, there were dropping out of nerve cells in the cortex and an acute reaction of the glia

10. Baker, A. B.: Cerebral Lesions in Hypoglycemia: Some Possibilities of Irrevocable Damage from Insulin Shock, Arch. Path. **26**:765-776 (Oct.) 1938.

11. Döring, G.: Zur Histopathologie und Pathogenese des tödlichen Insulinshocks, Deutsche Ztschr. f. Nervenh. **147**:217-227, 1938.

12. Kastein, G. W.: Insulinvergiftung; klinische und anatomischhistologische Beschreibung, Ztschr. f. d. ges. Neurol. u. Psychiat. **163**:342-361, 1938.

13. Leppien, R., and Peters, G.: Todesfall infolge Insulinshockbehandlung bei einem Schizophrenen, Ztschr. f. d. ges. Neurol. u. Psychiat. **160**:444-454, 1937.

14. Cammermeyer, J.: Ueber Gehirnveränderungen, entstanden unter Sakelscher Insulintherapie bei einem Schizophrenen, Ztschr. f. d. ges. Neurol. u. Psychiat. **163**:617-633, 1938.

elements. The anatomic lesions in the brains of these animals indicate that a single insulin shock approaching nine hours in duration may result in permanent damage to the cortex.

A third group of 6 monkeys were killed after they had been subjected during a period of several weeks to 9, 29, 31, 32, 33 and 40 insulin comas, respectively, each averaging from two and one-half to three hours in duration. In these animals extensive damage to nerve cells was found both in the cortex and in the basal structures. There was also a marked glial response, not only in the regions of damage to the nerve cells but also in the white matter of the cerebral and cerebellar hemispheres. Vascular changes were considered to be secondary.

An attempt is made to reconstruct the pathogenesis of these lesions resulting from insulin, and evidence is brought forward to show that they may best be considered due to the cumulative effect of each insulin shock rather than that any one lesion was caused by a single shock. It is stressed that even in the animal which received only 9 insulin comas cortical damage of a permanent character was observed.

It is suggested that the metrazol and insulin shock therapies are justified only when the beneficial clinical results outweigh the resulting permanent damage to the brain which these studies demonstrate.

AMPHETAMINE SULFATE–SODIUM AMYTAL TREATMENT OF SCHIZOPHRENIA

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Since 1936 we have been employing amphetamine (benzedrine) sulfate in the treatment of psychotic patients.[1] Shortly after the inception of our investigations we discovered that a more beneficial effect could be obtained, particularly in treatment of schizophrenia, when sodium amytal and amphetamine sulfate were administered in combination than when either of these drugs was used alone.

The present communication is concerned with the results obtained with this combined therapy during the past three years in a series of 80 patients with dementia praecox. A comparison is made with the responses of four control groups of patients: (1) 500 patients with schizophrenia treated by other routine procedures, (2) 50 patients with dementia praecox treated with sodium amytal alone, (3) 30 patients with dementia praecox treated with amphetamine sulfate alone and (4) 25 patients with manic-depressive psychosis treated by the combined amphetamine-amytal method.

PROCEDURE

In applying the combined therapy, we selected for treatment only those patients who after a careful preliminary study presented no physical contraindication. To each patient we gave 10 mg. of amphetamine sulfate and 0.2 Gm. of sodium amytal orally on different days to detect idiosyncrasy to either of these drugs.

The patients received an initial oral dose of 0.4 Gm. of sodium amytal, followed at intervals of one-half hour by oral administration of 0.2 Gm. of sodium amytal

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Read at the Ninety-Sixth Annual Meeting of the American Psychiatric Association, Cincinnati, May 23, 1940.

From the Department of Psychiatry, Syracuse University College of Medicine, and the Syracuse Psychopathic Hospital, Dr. Harry A. Steckel, Director.

1. Davidoff, E., and Reifenstein, E. C., Jr.: Treatment of Schizophrenia with Sympathomimetic Drugs: Benzedrine Sulfate, Psychiatric Quart. **13**:127-144 (Jan.) 1939; The Results of Eighteen Months of Benzedrine Therapy in Psychiatry, Am. J. Psychiat. **95**:945-969 (Jan.) 1939; Psychiatric Aspects of Amphetamine (Benzedrine) Sulfate Therapy, Dis. Nerv. System **1**:58-63 (Feb.) 1940; A Method of Studying Some of the Physiologic Actions of Benzedrine Sulfate, J. Lab. & Clin. Med. **23**:700-711 (April) 1938.

until narcosis was obtained. The average amount necessary was 0.6 to 1 Gm., although larger doses were required occasionally in the agitated states. The amphetamine sulfate was administered intravenously. The first dose was 10 mg. and the second and third 20 mg. If the patient exhibited no untoward reaction to these injections, larger doses were employed subsequently. The average daily dose was 40 mg.

At first the drugs were administered on alternate days. The patients received sodium amytal in the morning and were permitted to remain in narcosis for fifteen to twenty hours. On the morning of the following day they were given amphetamine sulfate. However, this regimen interfered with the daily routine program of the patients and occasionally reversed the sleep cycle. Therefore, in many cases the initial dose of sodium amytal was administered in the late afternoon, and the patients were allowed to sleep until the next morning. At that time amphetamine sulfate was injected. This method had the advantages of producing a normal sleep cycle, of tending to establish a better habit formation in regard to sleep and daytime activities and of permitting participation in the daily hospital program.

Certain additional variations in the regimen were necessary to adapt it to the individual patient. To excited patients, for example, the sodium amytal was administered daily for several successive days prior to the initial injection of amphetamine, and to depressed patients amphetamine was given daily on successive days before the administration of sodium amytal was begun. In an occasional case in which deep narcosis was not indicated, amphetamine sulfate intravenously or orally and sodium amytal orally were administered simultaneously or in fairly rapid sequence. These variations were utilized in the beginning, during the course or at the end of the period of treatment.

Because of the limited period of residence permitted patients in our institution, we have not employed the combined therapy with any patient for more than two months. The average period of treatment was three weeks.

In the series of 80 patients with dementia praecox receiving the combined therapy, we included only those for whom a definite diagnosis of schizophrenia was agreed on by all members of the staff. We were particularly interested, furthermore, in applying the treatment to patients whose illness was of shortest duration, in accordance with our previous experience. For these reasons the 80 patients represented a selected group.

In the present analysis of results, only those patients were considered to be favorably influenced by the therapy whose condition was designated as much improved and who were discharged after a staff conference. The criteria for judging this improvement involved consideration of the total coordinate reaction of the patient rather than the response in any particular phase or at any particular time, including specifically the improvement in coordination of mood, speech and motor activity, the increase in insight, general efficiency, accessibility and social adaptability and the decrease in asocial behavior.

ANALYSIS OF RESULTS

The results are indicated in table 1. Of the 80 schizophrenic patients treated with the combined therapy, 29, or 36 per cent, were discharged to their homes. In 51 patients the psychosis was of less than two years' duration, and 22, or 43 per cent, of these were discharged. In the

remaining 29 the psychosis was of more than two years' duration, and of these only 7, or 24 per cent, returned home.

The most favorable results were obtained in the group with early catatonia, in which 15, or 56 per cent, of the 27 patients were discharged. In the group with more prolonged catatonia, improvement was observed in only 1 of 6 patients (16 per cent). Poor results were obtained in the paranoid and the hebephrenic group irrespective of the duration of the disease. Five of the 10 patients with simple dementia praecox reacted favorably, regardless of the length of the psychosis.

TABLE 1.—*Results of Combined Amphetamine—Sodium Amytal Treatment for Dementia Praecox*

	Duration of Illness					
	Under 2 Years			Over 2 Years		
Type of Schizophrenia	Total Number	Number Improved	Per Cent	Total Number	Number Improved	Per Cent
Catatonic	27	15	56	6	1	16
Paranoid	9	2	22	16	3	19
Hebephrenic	11	3	27	1	0	
Simple	4	2	50	6	3	50
Total	51	22	43	29	7	24

Total number = 80; number improved = 29 (36 per cent)

TABLE 2.—*Results in a Control Group of Patients Treated by Routine Measures with Dementia Praecox*

	Percentage of Patients Discharged	
Type of Schizophrenia	Ill Under 2 Years (276 Patients)	Ill Over 2 Years (224 Patients)
Catatonic	23	18
Paranoid	27	12
Hebephrenic	26	1
Simple	33	33
Total	26	14

Total number = 500; number improved = 103 (20.6 per cent)

COMPARISON WITH CONTROL GROUPS

1. In order to evaluate the results obtained with the combined treatment, a comparison was made with the responses of 500 schizophrenic patients admitted consecutively from 1931 to 1936. The data for this control group are presented in table 2. Only 20.6 per cent were discharged to their homes, as compared with 36 per cent of the patients treated with amphetamine and amytal. When the control group was subdivided according to the length of psychosis, it was found that 26 per cent of those ill less than two years were discharged, as compared with 43 per cent of the treated patients who had been ill for a similar period, while only 14 per cent of the control patients with prolonged

psychoses were discharged, as compared with 24 per cent of those receiving combined therapy.

Of the patients whose illness was of less than two years' duration, those with the catatonic type showed the greatest difference, 23 per cent of the control patients being discharged home as compared with 56 per cent of the patients receiving the amphetamine-amytal treatment. In the groups with other types of dementia praecox, however, comparison of the treated and the control patients indicated that the combined therapy had produced no significant alteration in the statistics.

2. For purposes of comparison, we reviewed our results with employment of sodium amytal alone. Inasmuch as the sodium amytal alone had been utilized, for the most part, in treatment of schizophrenic patients who were excited or agitated, the data are not strictly comparable. Of 50 consecutive patients subjected to amytal narcosis alone, only 30 per cent were discharged to their homes. Of the 31 catatonic patients in this group, 32 per cent were discharged.

TABLE 3.—*Results of Combined Amphetamine—Sodium Amytal Treatment in Group of Patients with Catatonia of Less Than Two Years' Duration*

	Type	Total Number	Number Improved	Per Cent Improved
Combined therapy	Excited self-absorbed	27	15	56
Amphetamine alone	Only self-absorbed	30	12	40
Amytal alone	Only excited	31	10	32
Control group (other procedures)	Excited self-absorbed	73	17	23

3. Similarly, we examined our previous experience with use of amphetamine sulfate alone. Inasmuch as this treatment had been restricted to patients who were retarded or self absorbed, the results again are not entirely comparable. Of a group of 30 catatonic patients whose psychosis had been present for less than two years, 40 per cent were sent home. Comparison of the various therapies for the catatonic groups is indicated in table 3.

4. As an additional comparison, we evaluated the results of the amphetamine sulfate–sodium amytal therapy with the first 25 of our series of manic-depressive patients thus treated. Thirteen, or 52 per cent, of these patients were returned to their homes. The most favorable results were obtained in the group of 13 depressed patients, 9 of whom were discharged as recovered. The least satisfactory response was observed in the manic group of 6 patients, only 1 of whom was discharged. Three of 6 patients with mixed forms of mania recovered. The combined method seemed to be most effective in the treatment of patients with simple depression or retardation.

These results were compared with those obtained in 50 consecutive manic-depressive patients who did not receive this therapy. Of these, 42 per cent were discharged as recovered, as compared with the 52 per cent who received the combined therapy. A greater benefit resulting from the combined therapy was a reduction in the length of hospital residence from an average period of five weeks, for the control patients, to an average period of three weeks, for the amphetamine–amytal–treated patients. This indicated a 40 per cent acceleration in the rate of improvement. As in the case of dementia praecox, the combined therapy of amphetamine sulfate and sodium amytal proved to be superior to the use of either drug alone in the treatment of manic-depressive psychoses.

COMMENT

The combined use of amphetamine sulfate and sodium amytal is of value in the treatment of certain patients with incipient schizophrenia, particularly of the catatonic type. In the preceding data, we have used the criterion of eligibility for discharge in evaluating the combined therapy. In addition, other favorable alterations have been observed to result from this treatment. Patients have been rendered more compliant with the hospital regimen, more willing to discuss their problems and more accessible to investigation and the institution of all forms of therapy. This treatment aids in establishing more coordinate habit patterns. The patients treated by this method manifest improvement in their physical condition and a favorable modification in their mental status. The excited patients become more calm and tractable; the retarded patients become more alert and cooperative. Furthermore, the combined therapy, as we have applied it, allows for full utilization of other important therapeutic procedures, such as occupational therapy and psychotherapy. The combined treatment may be employed advantageously as a preliminary to the more energetic shock procedures. It may have prognostic significance by indicating the response to other therapy. It seems, therefore, that the amphetamine sulfate–sodium amytal treatment is a valuable adjunct to the hospital routine for the treatment of all patients with schizophrenia, manic-depressive psychoses and other types of psychoses (such as the alcoholic).

In previous communications [1] we have presented some of the theoretic considerations concerning the action of amphetamine sulfate and its use in combination with sodium amytal. In essence, the combined therapy permits one rapidly to alternate depression with stimulation of the nervous system, without the necessity of counteracting the effect of either drug by additional medication. This is presumed to produce in the central nervous system a cycle of alternating positive and negative shocks. In addition, the combination of amphetamine sulfate and sodium

amytal is employed to produce antagonistic effects on some functions of the nervous system, synergistic effects on other functions and certain coalitional effects which are not present when either drug is administered alone. These coalitional actions have been augmented at times by giving the drugs simultaneously. The ultimate result that has been sought through these actions is an alteration of the functions of the entire autonomic nervous system [2] and the lower centers coincident with an augmentation of the integrative governing functions of the voluntary nervous system which eventuates in greater adaptability of the personality to an environmental situation by increasing the number of available pathways of coordinate action.

The fact that many patients with early catatonia can be improved by the combined therapy raises theoretic considerations as to the nature of some of the catatonic disease processes. Of all psychoses, we have found the most favorable response to amphetamine in those patients suffering from acute toxic states. Many of our patients with early catatonia have responded in a similar manner. This suggests that some states of catatonia may be toxic reactions. The toxin may be either exogenous or endogenous (endocrine). Toxic processes are catabolic, and it is possible that in some catatonic patients, at least, the catabolic-anabolic balance is only temporarily distorted, with a catabolic predominance, which may be overcome by the drug therapy.

Furthermore, the combined therapy exerts its favorable effect through the action of amphetamine and amytal, both of which have actions on the autonomic nervous system and also on the voluntary nervous system. The catatonic patients responding to the therapy may have, therefore, an imbalance of the autonomic nervous system or of the voluntary nervous system or of both. There may be a disturbed or disjointed relationship in the pathways between the autonomic and the voluntary nervous system which can be influenced by drugs so that the isolated action of the vegetative system may be reintegrated into the main stream of coordinate activity. The disjuncture may exist between the cortical, the suprasegmental, the segmental and the peripheral level of the nervous system. The relation of disturbances in the autonomic nervous system to dysfunction of the endocrine glands must be considered.

With these considerations in mind, we feel that the combined therapy may (1) indicate the inherent plasticity of the individual organism, (2) reveal the potentialities for compensatory or anabolic restorative proc-

2. Kempf, E. J.: Psychopathology, St. Louis, C. V. Mosby Company, 1921. Spiegel, E.: Bulbocapnine-Benzedrine Antagonism, J. Pharmacol. & Exper. Therap. **63**:438-443 (Aug.) 1938. Myerson, A.: The Rationale of Amphetamine (Benzedrine) Sulphate Therapy, Am. J. M. Sc. **199**:729-737 (May) 1940.

esses, (3) initiate these favorable progressions and thus prevent detrimental delay, (4) accelerate or augment the recuperative trends already spontaneously initiated and (5) indicate the presence of reversible toxic factors or disturbances in the components of the nervous system.

SUMMARY

1. The results obtained with the combined amphetamine sulfate–sodium amytal treatment in 80 patients with schizophrenia are presented.

2. The response is compared with that in four control groups of patients.

3. The value of the combined therapy as part of the regimen in a psychiatric institution is discussed.

4. It is concluded that this method is of value in treatment of incipient dementia praecox of the catatonic type.

SWEAT MECHANISM IN MAN

STUDY OF DISTRIBUTION OF SWEAT FIBERS FROM THE SYMPATHETIC GANGLIA, SPINAL ROOTS, SPINAL CORD AND COMMON CAROTID ARTERY

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AND
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This report is based on a study of the distribution of sweat fibers to the skin. Zones of diminished or no sweating were observed after various operations—ganglionectomies, rhizotomies, ligation of the common carotid artery and chordotomies—and after lesions of the spinal cord other than operative. The patients were placed in a heating cabinet, and the starch-iodine method of Minor [1] was used as an indicator of sweating.

DISTRIBUTION AND CHARACTER OF ANHIDROSIS AFTER SYMPATHETIC GANGLIONECTOMY

We have studied the thermoregulatory sweating response in patients after removal of the superior cervical ganglion, the inferior cervical and first dorsal ganglia, the inferior cervical and first and second dorsal ganglia, and so on to and including the seventh dorsal ganglion. Also, there were cases in which the response was studied after removal of the first and second lumbar and second, third and fourth lumbar ganglia.

Our results were essentially in agreement with those of List and Peet [2] and will not be reiterated in detail, but we should like to emphasize certain facts, so that comparisons may be made with the results following rhizotomies.

From the Department of Surgery, Neurosurgical Service, State University of Iowa, College of Medicine.

1. Minor, V.: Ein neues Verfahren zu der klinischen Untersuchung der Schweissabsonderung, Deutsche Ztschr. f. Nervenh. **101**:302-308, 1927.

2. List, C. F., and Peet, M. M.: Sweat Secretion in Man: I. Sweating Responses in Normal Persons, Arch. Neurol. & Psychiat. **39**:1228-1237 (June) 1938; II. Anatomic Distribution of Disturbances in Sweating Associated with Lesions of the Sympathetic Nervous System, ibid. **40**:27-43 (July) 1938.

1. After removal of various ganglia from the superior cervical to the fourth lumbar, thermoregulatory sweating was abolished in zones that corresponded closely with the somatic segmental distribution.[3]

2. The zone of anhidrosis had remarkably cleancut boundaries, except after lumbar ganglionectomy. This was particularly true at the midsagittal plane after unilateral ganglionectomy. The division here between the sweating and the nonsweating side was knife edge in character, with no evidence of any overlapping across the midline.

3. After ganglionectomy the zone of anhidrosis was absolute and complete. We have never been able to elicit a single drop of sweat in such a zone as a result of central thermoregulatory activity. We observed, however, that sweating did occur in the axilla even when the inferior cervical and upper six dorsal ganglia were removed. We were puzzled by this phenomenon of sweating in the axilla until we discovered that any sympathectomized area of the skin will sweat if two skin surfaces are in contact. We found that if a sympathectomized arm is flexed sweating will occur in the antecubital fossa (M. B., fig. 1). A clenched hand will sweat in the creases of the palm. If the hand is held on the ipsilateral shoulder, sweating will occur on both surfaces of the skin in contact. We produced mild sweating on the sympathectomized face and neck by holding a dry hot water bottle against the skin. We refer to this as contact sweating, or sweating of the first order. It is evidence for local actvity of the sweat glands due to a thermal stimulus.[4] (Second order sweating is spinally controlled, while third order sweating is centrally controlled.) If the arm is held away from the body, sweating will be absent in these cases, but even then we have seen a few small beads of sweat appear in the axilla. We have sufficient evidence that this is not the result of impulses from the hypothalamus through residual sweat fibers but is purely local activity and may be activated months after sympathectomy and regardless of whether the latter is preganglionic or postganglionic. This is a fact that one should take into account when doing the sweating test. There are cer-

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3. After removal of the inferior cervical and first dorsal ganglia we found thermoregulatory anhidrosis on the ipsilateral half of the face and on only the lateral half of the ipsilateral upper extremity. Removal of the inferior cervical and upper two dorsal ganglia has consistently resulted in complete thermoregulatory anhidrosis of the ipsilateral upper extremity.

4. After sufficient time has elapsed for thorough degeneration of postganglionic fibers, pilocarpine sweating will no longer occur in a sympathectomized zone. Contact sweating will occur in such a zone after administration of pilocarpine. As it occurs without pilocarpine, however, the result in this case may not be related to pilocarpine.

While we realize that the phenomenon of so-called imperceptible sweating, or skin evaporation, must be considered, we believe that the character and magnitude of the response we describe indicate actual activity of the sweat glands.

tain areas over the body that usually sweat abundantly, i. e., the forehead, upper lip, neck, axilla, areola of the nipple (particularly in the female), palm of the hand and popliteal region. Local, or first order, sweating can be brought out in these areas rather easily in the manner already described.

4. After lumbar ganglionectomy we usually obtained diminished but definite sweating to or just below the knee, with absence of sweating

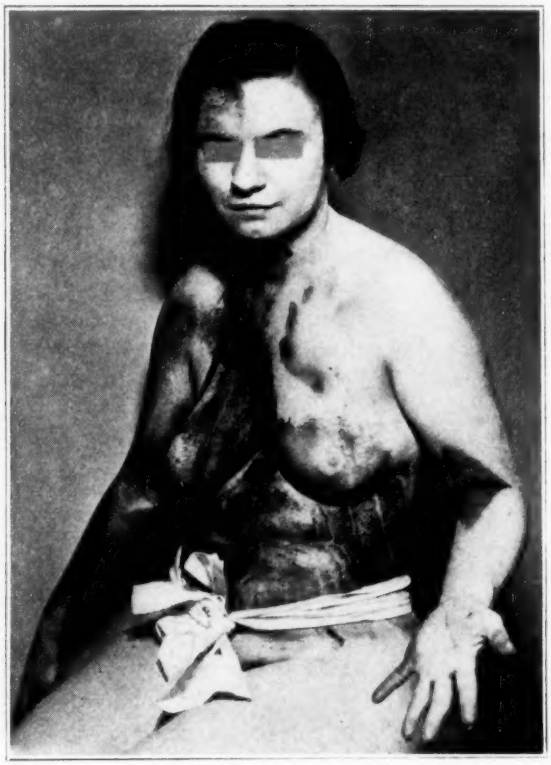

Fig. 1 (M. B.).—A starch-iodine thermoregulatory sweating test three hundred and eighty-seven days after the removal of the inferior cervical and upper three dorsal ganglia on the left.

While in the heat cabinet, the patient kept the fingers of the left hand in contact with the left side of the chest. Moisture was produced where skin was in contact with skin, i. e., on the fingers and chest, axilla and antecubital fossa. Evidence of moisture can be seen also in the creases of the left hand. There was no sweating in the sympathectomized zone when the forearm was maintained in extension and away from the body.

below this level. We could discern no particular difference in the result after removal of the first and second lumbar ganglia and the result after removal of the second, third and fourth lumbar ganglia.

5. The possibility of regeneration after sympathectomy has been considered particularly with reference to an explanation for so-called relapses in Raynaud's disease. Smithwick [5] has designed an operation in an attempt to prevent the possibility of regeneration. He reported cases in which "relapse" was believed to be attributed to regeneration. We feel it significant, however, that his evidence for regeneration was

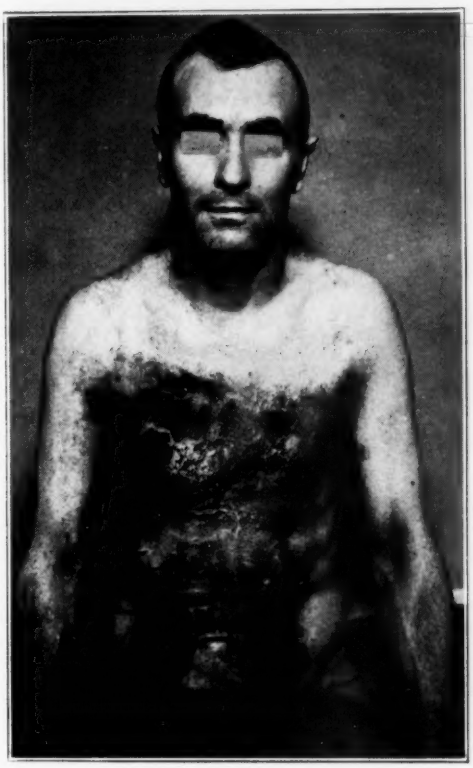

Fig. 2 (W. P., case 2).—Thermoregulatory sweating test fifty-five days after section of the posterior roots bilaterally from the eighth cervical to the fifth thoracic, inclusive, and the anterior roots bilaterally from the first to the fifth thoracic, inclusive. There is marked hyphidrosis to the level of the third dorsal segment, but many drops appeared over the shoulders and a few on the upper lip and chin. Of 6 patients, this patient showed the most marked hyphidrosis after section of the upper five anterior thoracic roots.

based on cutaneous resistance and the psychogalvanic reflex. We do not believe that this indicator is nearly so reliable as the Minor starch-iodine test [1] for thermoregulatory sweating depending on central

5. Smithwick, R. H.: Surgical Intervention on the Sympathetic Nervous System for Peripheral Vascular Disease, Arch. Surg. **40**:286-306 (Feb.) 1940.

impulses. In our patients subjected to cervicodorsal ganglionectomy on whom we made the thermoregulatory and pilocarpine sweating tests, we have never seen the slightest evidence that regeneration had occurred up to twenty months. The thermoregulatory sweating test has indicated no regeneration to the lower extremity after lumbar ganglionectomy

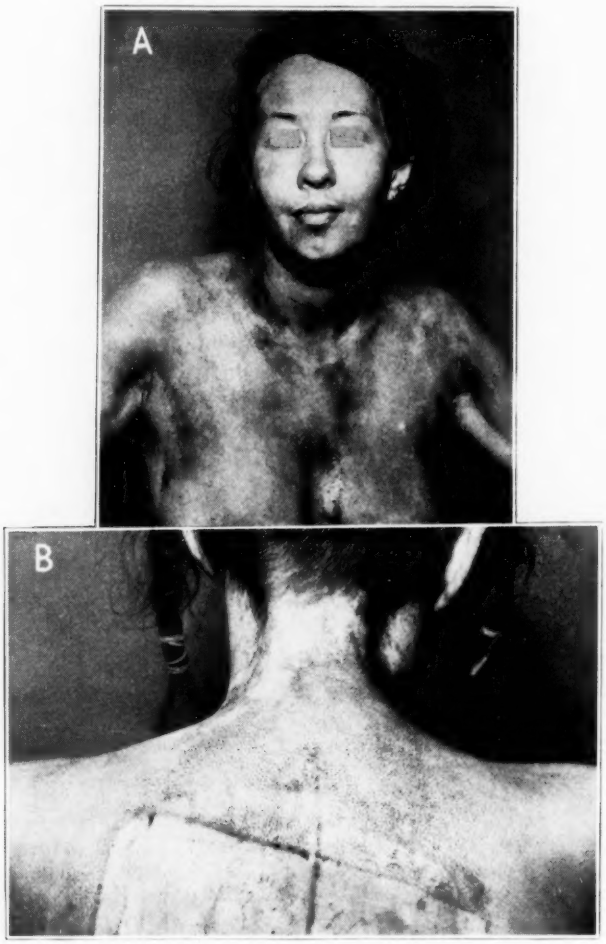

Fig. 3 (H. E., case 3).—*A*, thermoregulatory sweating test thirty-nine days after bilateral section of the anterior and posterior roots from the first to the fifth thoracic, inclusive, and chordotomy at the third thoracic segment as indicated in figure 9. Sweat appeared on the neck and below. It was absent on the face, except for a few droplets above and below the lips. We do not believe that the chordotomy influenced sweating in any way.

B, rear view, showing evidence of sweating on the back of the neck. The square area without sweating is the place where dressing had been applied.

up to eight months. These postoperative periods are smaller, however, than those in Smithwick's cases.

DISTRIBUTION OF ANHIDROSIS AFTER RHIZOTOMY

Section of Posterior Roots.—Two patients were studied after section of the posterior roots only from the first to the fifth thoracic, inclusive. No changes from the normal were elicited. One patient

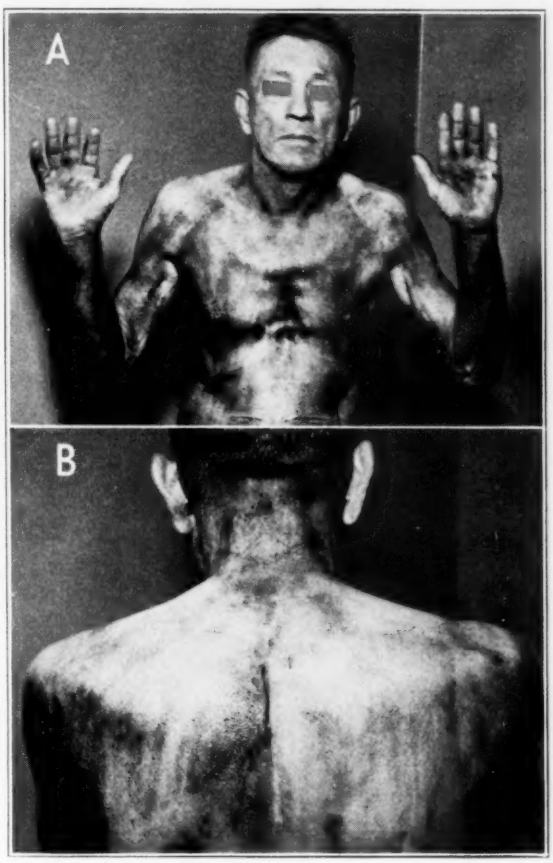

Fig. 4 (L. W., case 4).—*A*, thermoregulatory sweating test eighty days after bilateral section of the anterior and posterior roots from the first to the fifth thoracic, inclusive, and chordotomy at the third thoracic segment as indicated in figure 9. Sweating was practically abolished on the face and slightly diminished to the level of the third dorsal segment. A few droplets of sweat appeared on the forehead at the hair line and above and below the lips. The chordotomy had no influence on sweating.

B, rear view, showing diminished sweating down to the third dorsal segment but a fair amount on the back of the neck.

was studied in whom posterior roots from the first to the tenth thoracic, inclusive, were sectioned bilaterally. No discernible alteration in sweating was noted.

Section of Anterior Roots.—Six patients (cases 2 to 6) were studied after section of both posterior and anterior roots from the first to the

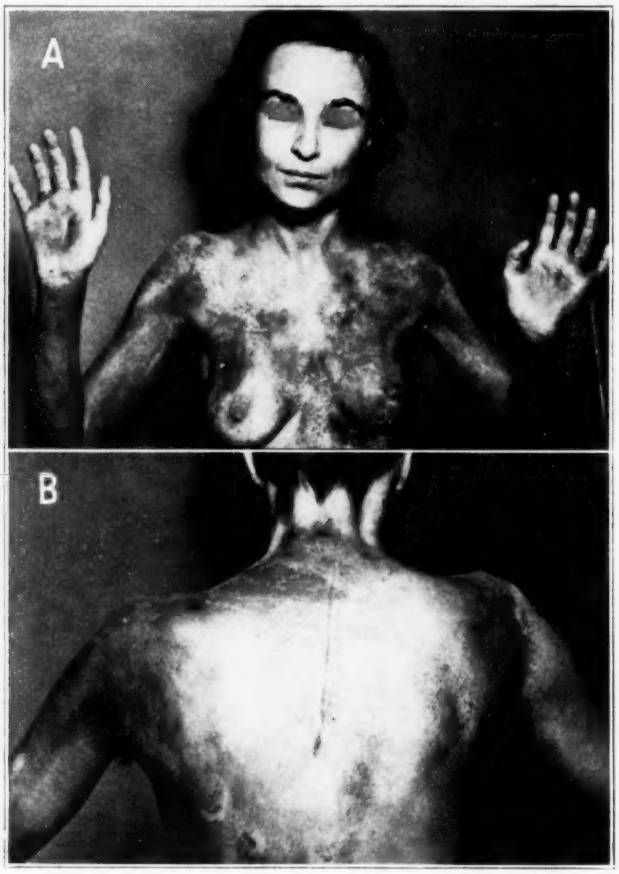

Fig. 5 (L. C., case 5).—*A*, thermoregulatory sweating test forty-six days after bilateral section of the anterior and posterior roots of the first to the fifth thoracic nerve, inclusive, and chordotomy at the third dorsal segment as indicated in figure 9. Sweating was abolished on the face and diminished in an irregular area down to the level of the third dorsal segment. Sweating on the arms and hands was normal.

B, rear view, showing fairly good sweating on the back of the neck.

fifth thoracic, inclusive (figs. 2 to 6). In 5 of these patients bilateral chordotomy was also done at the third thoracic level [6] according to the

6. These procedures were carried out in an attempt to benefit patients with advanced essential hypertension.

pattern shown in figure 9. In 1 patient (case 2, fig. 2) only the rhizotomy was done. After studying the sweating reactions of these patients, we believe that the chordotomies did not complete the results of the upper dorsal rhizotomies,[7] and this is borne out by the results in case 2, figure 2. Hence the results in these patients may be accepted as those which occur when the upper five anterior thoracic roots are severed bilaterally.

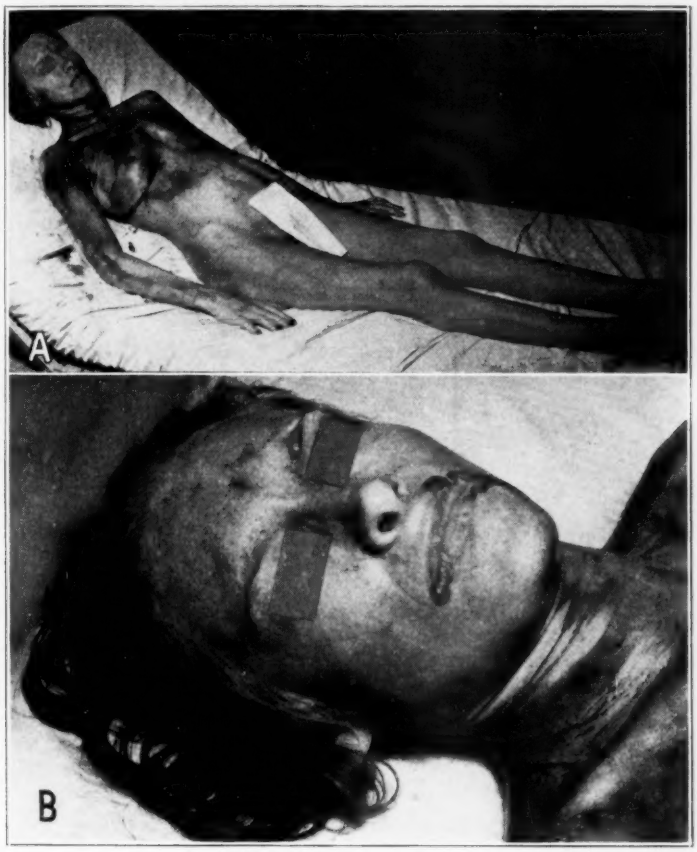

Fig. 6 (V. S., case 6).—*A*, thermoregulatory sweating test one hundred and sixteen days after bilateral section of the anterior and posterior roots of the first to the fifth thoracic nerve, inclusive, and chordotomy at the third dorsal segment as indicated in figure 9.

B, closer view of the face, showing droplets on the forehead and face, more marked on the right than on the left, with a definite line of demarcation at the middle of the forehead. The discoloration about the lips is an artefact.

7. Case 6 may be an exception. It is the only case of this group in which chordotomy influenced sweating, and is given special consideration in the section on chordotomy.

One patient (case 7, fig. 7) was studied after section of the anterior roots bilaterally from the third thoracic to the second lumbar, inclusive, for essential hypertension.

One patient (case 8, fig. 8) was studied after section of the anterior roots from the third to the seventh thoracic, inclusive, on the right and from the third to the ninth thoracic, inclusive, on the left. The operation was done for relief of Raynaud's disease of the upper extremities. The case is important enought to report in some detail.

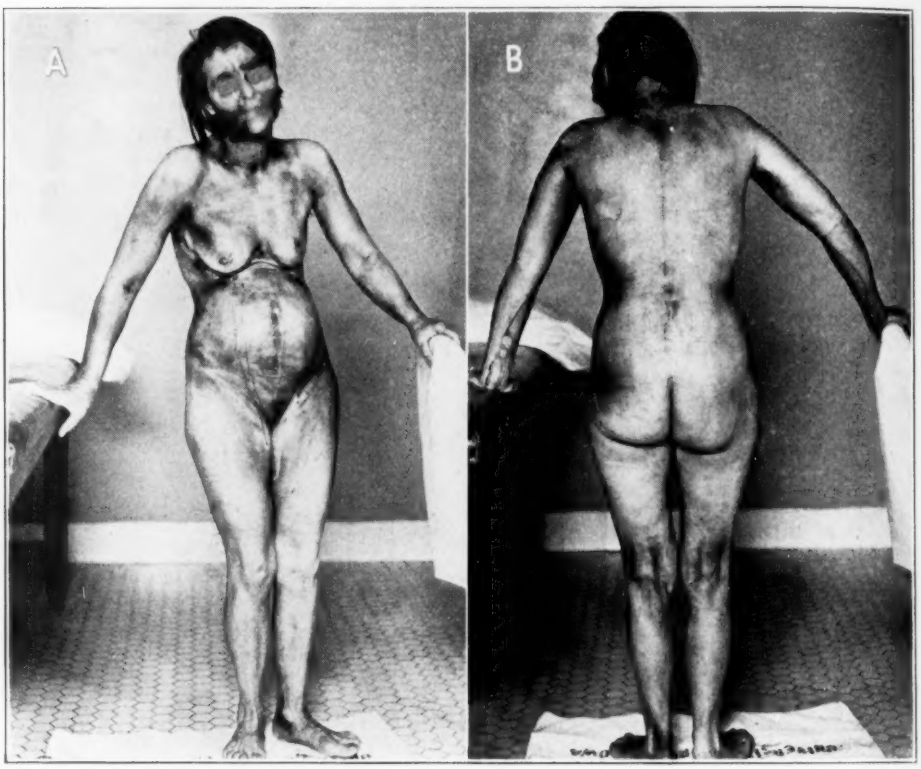

Fig. 7 (M. P., case 7).—*A*, thermoregulatory sweating test twenty-one months after bilateral section of the anterior roots of the third thoracic to the second lumbar nerve, inclusive. There is hyphidrosis on the thighs, legs and right foot, but a surprising amount of sweating is preserved.

B, rear view, showing good sweating in the popliteal fossae and on the left foot and ankle.

CASE 8.—R. C., a white man aged 27 with Raynaud's disease, on Feb. 8, 1940 underwent section of the anterior roots of the third to the seventh thoracic segment, inclusive, on the right and of the third to the ninth thoracic segment, inclusive, on the left. (This was carefully determined at operation and checked by roentgen study of silver clips after operation.) He exhibited paralysis of the lower extremities

and bladder after operation but gradually recovered good function. Sensation to pain and temperature for a time was largely abolished, with retention of sense of position and sensibility to touch. We attributed this to ischemic paralysis of the cord below the third thoracic level.

A sweating test done on February 21, thirteen days after operation, revealed a definite level at the sixth dorsal segment above which sweating was abundant [8] and below which it was totally absent (fig. 8).

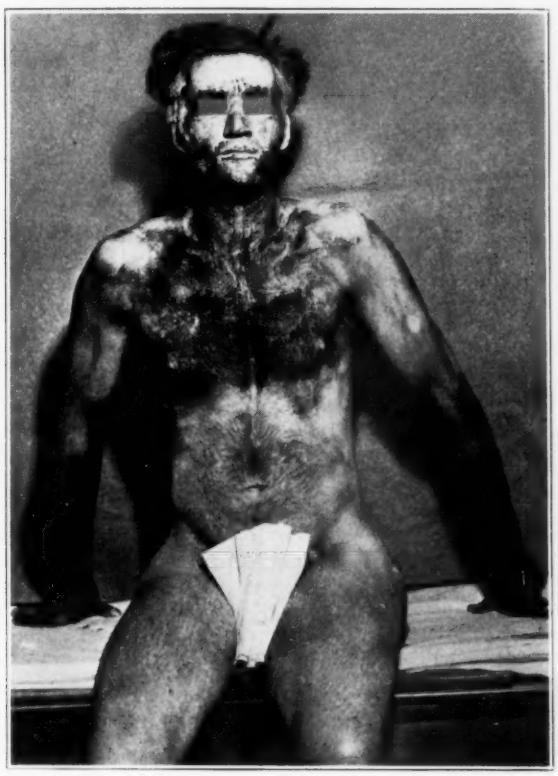

Fig. 8 (R. C., case 8).—Thermoregulatory sweating test thirteen days after section of the anterior roots of the third to the seventh thoracic nerve, inclusive, on the right and the third to the ninth thoracic nerve, inclusive, on the left. At this time there was clinical evidence of ischemia of the cord. There were complete anhidrosis below the sixth dorsal segment and abundant sweating above, with a fairly well defined level at the sixth dorsal segment. The apparent hyphidrosis over the shoulders, arms and face is due to the fact that sweating was so abundant that it washed away some of the starch-iodine preparation. See case report for the results of a subsequent sweating test.

8. When thermoregulatory sweating is abolished on a large area of skin, the remaining skin appears to sweat more profusely than normal. This is probably a compensatory reaction.

A sweating test on March 9, thirty days after operation and after marked recovery in sensory and motor function, showed abundant sweating over the entire body except for hyphidrosis about the ankles and feet. There was not the slightest indication of hyphidrosis in the distribution of rhizotomy.

COMMENT ON RESULTS FOLLOWING ANTERIOR RHIZOTOMY

After the upper five anterior thoracic roots were cut bilaterally, thermoregulatory sweating of the face was almost entirely abolished. Hyphidrosis was discernible as low as the second thoracic segment, both front and back. The hyphidrosis was marked in 2 cases (figs. 2 and 4), but fair sweating appeared on the neck in the other cases. Sparse beads of sweat appeared on the face, particularly about the upper lip and the cheeks (note especially fig. 6*B*). In all of these cases the arms and hands sweated profusely.

In case 7 (fig. 7) it was surprising to find no greater reduction of sweating after the anterior roots from the third thoracic to the second lumbar, inclusive, were cut bilaterally. One might propose that the preganglionic fibers had regenerated after twenty-one months. An alternative explanation is that after this period the supply from the second anterior thoracic roots is sufficient to activate postganglionic fibers down to the ankle.

The first anterior thoracic roots appear to supply no sweat fibers to the sympathetic chain. We have recently deduced evidence for this, which will be submitted in another publication. Also, the work of Smithwick [9] bears this out. Whether the preganglionic sympathectomy as done by Smithwick, and also by Telford,[10] for Raynaud's disease is a complete sympathectomy or not depends on the assumption that the first anterior thoracic root contains no sympathetic fibers to the upper extremity, inasmuch as the rami of the first thoracic root are left intact.

The second anterior thoracic roots appear to contain many sweat fibers, or at least ultimately to activate many sweat glands from the sixth dorsal segment upward. In cases 15 and 16, under the section on chordotomy, it will be noted that section of the second anterior thoracic roots alone results in definite diminution of sweating over the face. The diminution was unequal, however, on the two sides. Section of the third anterior thoracic roots only did not result in noticeable diminution of sweating.

One learns from case 8 that the second anterior thoracic root activates abundant thermoregulatory sweating from the skin level of the sixth

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9. Smithwick, R. H.: Modified Dorsal Sympathectomy for Vascular Spasm (Raynaud's Disease) of the Upper Extremity: A Preliminary Report, Ann. Surg. **104**:339-350, 1936; footnote 5.

10. Telford, E. D.: The Technique of Sympathectomy, Brit. J. Surg. **23**:448-450, 1935; Sympathetic Denervation of the Upper Extremity, Lancet **1**:70-72, 1938.

dorsal segment upward, the conclusion being accepted that the roots of the first thoracic nerve contain no sweat fibers. This case also teaches that the anterior roots from the tenth thoracic to the third lumbar activate sufficient sweating to meet this level, so that interruption of the roots from the third to the ninth thoracic does not noticeably diminish sweating. It certainly did not diminish sweating on the upper extremities. This is not in agreement with Langley's [11] conclusion that the upper extremities are supplied by the roots of the fourth to the tenth thoracic nerve.[12]

These studies after section of the anterior roots provide further clinical verification of a fact already known. The preganglionic neurons in any given anterior root are in functional connection with a great number of postganglionic neurons. Consequently, a single root is represented in a number of sympathetic ganglia, and hence has an extensive peripheral distribution. The results of the sweating test after rhizotomy are complementary to those obtained by directly stimulating an anterior root.

Foerster [13] made some observations on sweating after stimulating anterior roots. By stimulating the anterior root of the first thoracic nerve sweating began over the face. By increasing the stimulus the level of sweating was caused to progress downward, including the neck and even the upper portion of the thorax.[14] By stimulating the anterior root of the second thoracic nerve sweating began on the neck and thorax, while a stronger stimulus brought it out in the face. Stimulation of the anterior root of the third thoracic nerve caused sweating to begin in the axilla. Stimulation of even the sixth anterior thoracic root caused sweat to appear over the arm. His observations on vasoconstriction and piloerection after stimulation were essentially in agreement with those on sweat secretion. He has never observed any such changes by stimulating the anterior root of the seventh cervical nerve or those higher or by stimulating the anterior roots below the third lumbar. These results are interesting in that they demonstrate

11. Langley, J. N.: On the Origin from the Spinal Cord of the Cervical and Upper Thoracic Sympathetic Fibers, with Some Observations on White and Grey Rami Communicantes, Phil. Tr. Roy. Soc., London, s.B **183**:85, 1892.

12. The anterior thoracic roots which supply sympathetic fibers to the upper extremity have been variously indicated, as follows: third to ninth thoracic (Ascroft [19]); third (?) to eighth thoracic (White, J. C.: The Autonomic Nervous System, New York, The Macmillan Company, 1935, p. 60); second to sixth thoracic, and occasionally lower (Fulton, J. F.: Physiology of the Nervous System, New York, Oxford University Press, 1938, p. 218), and second to sixth or seventh thoracic (Foerster [13]).

13. Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 5, pp. 32-54.

14. This is not in agreement with the work of Smithwick or with our findings, which we shall submit in a later publication.

not only the extensive peripheral representation of each root but also the variation in the extent of the activated skin zone above and below the distribution with the strength of stimulus.

Foerster also stated that after cutting anterior roots from the third cervical to the third thoracic there was no sweating over the face. After cutting the roots of the tenth thoracic to the fifth sacral nerve there was no sweating in the second lumbar to the fifth sacral segments. Our results were not exactly in agreement with these, since we obtained sweating on the back of the neck and small amounts on the face after cutting the first to the fifth thoracic root, inclusive. In this case one would have to take into consideration the fact that the response varies with the strength of stimulus. Foerster stated that he believed there

Foerster's Table Showing Ganglia Represented by Each Anterior Root

Segment of Cord	Cervical Ganglia	Thoracic Ganglia	Lumbar Ganglia	Sacral Ganglia
C VIII	Superior	.....	.....	.....
Th I	Superior	.....	.....	.....
Th II	Superior	.....	.....	.....
Th III	Superior, middle, inferior	$Th_1Th_2Th_3$	.....	.....
Th IV	Middle, inferior	$Th_1Th_2Th_3$ $Th_4Th_5Th_6$	.....	.....
Th V	Inferior	Th_1-Th_9	.....	.....
Th VI	Inferior	Th_1-Th_9	.....	.....
Th VII	Inferior	Th_1-Th_9	.....	.....
Th VIII	.....	Th_5-Th_{11}	.....	.....
Th IX	.....	Th_6-Th_{12}	L_1	.....
Th X	.....	Th_7-Th_{12}	L_1-L_5	.....
Th XI	.....	Th_9-Th_{12}	L_1-L_5	S_1-S_2
TH XII	.....	Th^{10}-Th^{12}	L^1-L^5	S^1-S^5
L I	.....	Th_{11}-Th_{12}	L^1-L^5	S^1-S^5
L II	.....	Th_{12}	L_1-L_5	S_1-S_5
L III	.....	.....	.....	S_1-S_5

were no sweat fibers in the eighth anterior cervical root, but because of other functions he included the root in his table, which is given here. Again, we obtained some sweating about the ankles and popliteal fossae even after cutting the anterior roots from the third thoracic to the second lumbar, inclusive, on both sides. Here the possibility of sweat fibers in the third lumbar root could explain the difference in results, or, as already mentioned, the roots of the second thoracic nerve might activate the whole chain a long time after operation.

Foerster [13] (page 44) prepared the accompanying table,[15] in which he gave the number of ganglia represented by each anterior root.

15. The table has also been recorded in the following two papers, in which are discussed essentially the same principles as those given by Foerster:[13] Guttmann, L.: Die Schweiss-sekretion des Menschen in ihren Beziehungen zum Nervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **135**:1-48, 1931. Guttmann, L., and List, C. F.: Zur Topik und Pathophysiologie der Schweiss-sekretion, ibid. **116**:504-536, 1928.

On the basis of case 8 we should have to modify this table at least in the following way: The anterior roots of the second thoracic nerve contain fibers to and including the sixth dorsal ganglion.

Stimulation of anterior roots has been carried out in animals also. Langley [11] demonstrated that for the cat dilator fibers of the pupil reside in the first three anterior thoracic roots. Those innervating the nictitating membrane, submaxillary glands and vessels of the head course through the upper five anterior thoracic roots. The pilomotor nerves of the face and neck reside in the upper seven thoracic nerves. Pilomotor, secretory and vasomotor fibers to the forefoot reside in the anterior roots from the fourth to the ninth thoracic, the preganglionic fibers terminating in the stellate ganglion.

Another approach to the problem of segmental distribution consists of a study of retrograde degeneration of lateral horn cells. Gagel, cited by Foerster [13] (page 34), found marked retrograde degeneration of lateral horn cells in the eighth cervical and first and second thoracic segments after removal of a superior cervical ganglion.

From an anatomic standpoint, Billingsley and Ranson [16] concluded that the preganglionic fibers of any given spinal nerve root have a more extensive connection with the peripheral ganglia than has any single fiber in the root. Ranson and Billingsley [17] stated:

> The sympathetic trunk is to be looked upon as a series of more or less segmentally arranged ganglia bound together by fibers from the white rami. Above the sixth thoracic ganglion these fibers are chiefly ascending, below the tenth descending, but between the sixth and tenth both ascending and descending fibers are present.

Individual Variations.—Variations are more easily studied at the upper and lower ends of the sympathetic domain in the cord. Foerster [13] (page 45) obtained dilatation of the pupil by stimulating the anterior roots of the eighth cervical, the first thoracic or the second thoracic nerve. In cases in which stimulation of the eighth anterior cervical root gave a strong response, that obtained from the second thoracic was weak and vice versa. Stimulation of the first thoracic root always resulted in the most marked response. Foerster also found variations in regard to the content of sympathetic fibers in the third lumbar root.

In 5 patients in whom one of us (O. H.) sectioned the anterior and posterior roots of the first to the fifth thoracic nerve, inclusive and bilaterally, the Horner syndrone was variable. In 3 cases there were

16. Billingsley, P. R., and Ranson, S. W.: On the Number of Nerve Cells in the Ganglion Cervicale Superius and of Nerve Fibers in the Cephalic End of the Truncus Sympatheticus in the Cat and on the Numerical Relations of Pre-Ganglionic and Post-Ganglionic Neurones, J. Comp. Neurol. **29**:359-384, 1918.

17. Ranson, S. W., and Billingsley, P. R.: The Thoracic Truncus Sympathicus, Rami Communicantes and Splanchnic Nerves in the Cat, J. Comp. Neurol. **29**:405-439, 1918.

bilateral miosis and ptosis. In 2 cases this result was unilateral, being on the right in 1 case and on the left in the other. In 2 of these cases (2 and 4) hyphidrosis in the third dorsal sergment was definitely more marked than in the other cases. This could be evidence of a variation. However, in cutting spinal roots one must take into consideration a possible embarrassment of blood supply to the cord. We do not believe this accounts for the difference to which we refer.

Studies in root distribution of sympathetic fibers leads to an important practical conclusion. Section of anterior roots alone designed to serve as a sympathectomy is impractical. Although rhizotomy is an easier task than ganglionectomy and offers the advantage of a bilateral operation in one stage, the necessary extensiveness of the laminectomy and the number of roots which would have to be sectioned in a given case constitute a greater disadvantage.

The effects on the viscera of stimulation of various peripheral sympathetic trunks, such as the splanchnic, have been recorded, but, as Foerster [13] has pointed out (page 44), no one has studied these responses by stimulating the anterior roots, and indeed the number of anterior roots contributing to the splanchnic trunks, for example, has not been clearly established.

On reference to Foerster's table it will be seen that in order to eliminate the ganglia from which the splanchnic trunks take origin one would have to begin with at least the roots of the fourth thoracic nerve. It is likely that section of the anterior roots from the sixth thoracic to the second lumbar, as practiced in the treatment of essential hypertension, is far from constituting a complete splanchnicotomy. Our results, particularly in case 8, make this statement even more evident. It is also evident that a few remaining sympathetic preganglionic neurons may cause marked responses because of their widespread connections with postganglionic neurons and because of the mechanism of compensatory reaction.

INFLUENCE OF VARIOUS TYPES OF CHORDOTOMY ON SWEATING

Five cases (2 to 6) referred to in the section on rhizotomy are included here. The chordotomy in these cases was done at the third thoracic level according to the pattern shown in figure 9. Four of the patients retained good motor function in the lower extremities. Sensibility to pain and temperature was lost to levels reaching as high as the pelvis.[18] Bladder function was impaired for one to two weeks Chordotomy had no influence on sweating in 4 cases. The fifth case (6) in this group will be reported in detail subsequently.

18. These results are in keeping with the views given in a recent publication (Hyndman, O. R., and Van Epps, C.: Possibility of Differential Section of the Spinothalamic Tract: A Clinical and Histologic Study, Arch. Surg. **38**:1036-1053 [June] 1939).

CASE 9 (L. A.).—Thromboangiitis obliterans with pain in the left leg. Chordotomy was done on the right side at the third thoracic level according to the pattern shown in figure 10 and the third anterior thoracic root on the right was cut, but neither this nor the chordotomy had any influence on sweating.

CASE 10 (G. D.).—Extensor spasticity of the right lower extremity, of central origin. Unilateral chordotomy was done on the right at the third thoracic level according to the pattern shown in figure 11, except that in this case the section was begun at the dentate ligament. The third anterior thoracic root on the right was cut, but neither this nor the chordotomy had any influence on sweating.

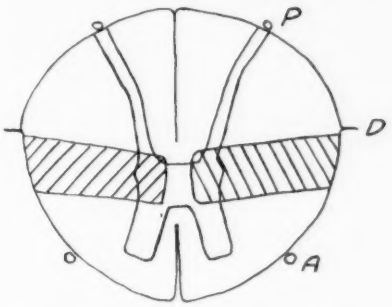

Fig. 9.—Diagram to illustrate manner in which chordotomy was done. Cross-hatching indicates the region in which the section was made. The anterior columns and part of the spinothalamic tracts are spared in this type of chordotomy.

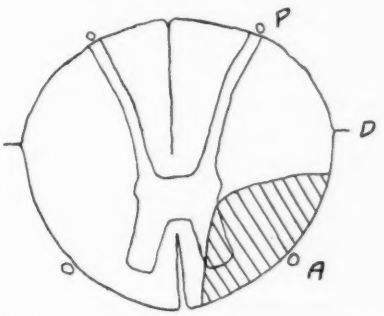

Fig. 10.—Diagram to illustrate manner in which chordotomy was done. Cross-hatching indicates the region in which section was made. This type of chordotomy is intended to interrupt the spinothalamic (pain) tract completely with a minimal section of the cord. If the chordotomy is to be made bilaterally, a section equivalent to this is made on the opposite side.

CASE 11 (A. S.).—Essential hypertension. Bilateral chordotomy done between the seventh and the eighth cervical segment according to the pattern shown in figure 11 had no influence on sweating.

CASE 12 (L. K.).—Gastric crisis of tabes. Chordotomy done between the fifth and the sixth cervical segment on the left and between the sixth and the seventh cervical segment on the right according to the pattern in figure 11 had no influence on sweating.

CASE 13 (L. E.).—Essential hypertension. Bilateral chordotomy done between the eighth cervical and the first thoracic segment according to the pattern in figure 10 had no influence on sweating.

CASE 14 (S. K.).—Essential hypertension. Bilateral chordotomy at the first thoracic segment according to the pattern in figure 9 had no influence on sweating.

CASE 15 (L. W.).—Essential hypertension and migraine. Bilateral chordotomy was done at the second thoracic segment according to the pattern in figure 10. The second anterior thoracic roots were cut in making the sections. Sweating on both sides of the face was diminished. That on the left side of the face was about 10 per cent of that on the right, and there was a definite line of demarcation in the midsagittal plane. (The left eye showed the characteristics of Horner's syndrome.) Otherwise sweating was not influenced.

CASE 16 (L. B.).—Gastric crisis of tabes. Bilateral chordotomy was done at the second thoracic segment according to the pattern in figure 10. The filaments of the second anterior thoracic roots were cut. Sweating was estimated as being about 25 per cent of normal on the right above the second dorsal level and 50

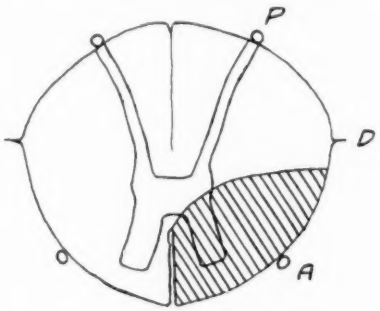

Fig. 11.—Diagram to illustrate manner in which chordotomy was done. Cross-hatching indicates the region in which section was made. This section interrupts the spinothalamic tract and the anterior column.

per cent of normal on the left above the same level. There was a definite line of demarcation in the midsagittal plane of the face. Otherwise sweating was not influenced.

In the preceding 12 cases in which chordotomy was done there was no clinical evidence of any marked damage to the pyramidal tracts at a spinal level. In the following 2 cases there was clinical evidence of marked damage to the pyramidal tracts, and sweating was likewise considerably influenced as a result of the chordotomy.

CASE 6 (V. S., fig. 6).—A white woman of 28 had essential hypertension. On April 14, 1939 the anterior and posterior roots were sectioned bilaterally from the first to the fifth thoracic, inclusive. Bilateral chordotomy was done at the third thoracic segment, as indicated in figure 9. The blood pressure fell rather low. She responded to administration of fluids, became conscious and did well for several hours. Then suddenly she screamed, jabbered incoherently and presented involuntary jerking of the upper extremities. The lower extremities and the right arm became flaccid, while the left arm continued to jerk and was in flexor spasm. She

recovered consciousness the next day, and in two weeks the arms recovered. The lower extremities were paralyzed except for ability to wiggle the toes and presented hyperactive knee and ankle jerks, ankle clonus and plantar extension of the great toes. The impression was that thrombosis of the sagittal sinus may have developed. She continued to improve, so that in four months she voided voluntarily and walked, with support. At this time pain and temperature sensibility to the hips were 50 per cent normal, and touch sensation was 100 per cent normal. Sensory loss due to upper dorsal rhizotomy corresponded with the anatomic distribution. A sweating test, carried out on August 17 under a heat cradle, gave a definite level just above the umbilicus below which there was no sweating (fig. 6*A*). The chest, arms and neck sweated normally, and there were droplets over the face. There was definitely less sweating on the left side of the face (fig. 6*B*). She exhibited a Horner syndrome only on the left.

Analysis of this case is difficult. We believe that the total absence of sweating below the level of the eighth dorsal segment must be attributed to the chordotomy. It should be noted that the chordotomy was more damaging to the pyramidal tracts than it was in the other patients, who sweated normally. The spinothalamic tracts were only mildly damaged, and the anterior columns were spared. The chordotomy was done at the third dorsal segment, and one might conclude that the sweat fibers in the cord were completely interrupted at this level; however, the upper five anterior thoracic roots were also severed bilaterally. The only explanation we can give is that fibers coursing through the roots of the sixth, and possibly the seventh, thoracic nerve were spared and account for all the sweating that was preserved. Such fibers apparently do not course downward in the sympathetic chain. On December 19 this test was repeated in the inductotherm cabinet. In one hour the patient's temperature rose from 98.0 to 102 F. The result with reference to sweating was the same as in the previous test.

CASE 17 (F. C.).—A white man aged 52 had syphilis of the central nervous system with unendurable lightning pains of many years' duration. On Dec. 8, 1939, bilateral anterior chordotomy was done between the seventh and the eighth cervical segment. The cord was about one-half to two-thirds the normal size, as is usually the case with tabetic cords. The operator suspected that he had injured the anterior spinal artery during the procedure. The cataract knife was inserted 1 to 2 mm. anterior to the dentate ligament and was brought out at the anterior median fissure. Sensation to pain and temperature was lost to the third dorsal segment. (Twenty-four days later it dropped to the level of the xiphoid process.) Touch sensation was not impaired. The right lower extremity remained permanently and flaccidly paralyzed and without deep reflexes until death, from intercurrent infection, on Jan. 5, 1940. Voluntary movement and strength of the left lower extremity were greatly impaired.

A sweating test, on Jan. 2, 1940, revealed that thermoregulatory sweating was abundant upward from a level midway between the xiphoid process and the umbilicus and was equal on the two sides. Below this level sweating was completely absent.

This result is unusual, as chordotomy at the eighth cervical segment caused abrupt and well defined cessation of sweating at the cutaneous

level of the seventh dorsal nerve, there being no sweating below this level and abundant sweating above. Evidently, sweat fibers to the roots of the second, and possibly the third, thoracic nerve remained intact, and this would be sufficient to activate all the sweating present. In this, as in case 6, the anhidrosis following chordotomy was associated with severe damage to the pyramidal tracts.

ANALYSIS OF THE RESULTS IN CASES OF CHORDOTOMY

Complete anterior chordotomy which severed the spinothalamic tracts and the anterior columns had no detectable influence on thermoregulatory sweating. Two patients (cases 6 and 17) who alone sustained severe damage to the pyramidal tracts demonstrated a definite effect of the chordotomy on sweating.

By referring to case 8 and to case 19, which is cited later, it may be indirectly concluded that no sweat fibers reside in the posterior columns.

Thus we conclude that sweat fibers, and no doubt all fibers of the sympathetic system, reside close to the pyramidal tracts anteriorly or may to some degree be interspersed with the pyramidal fibers. Our results are in general agreement with the location of the tract as indicated by Foerster [18] (page 224) and also by Ascroft [19] (in a diagram after Foerster).

INFLUENCE ON SWEATING OF LESIONS OF THE CORD OTHER THAN OPERATIVE

Case 18 (C. S.).—A white youth aged 18 had progressive loss of sensory and motor function below the second thoracic segment for two months. By Sept. 29, 1939 pain and thermal sense were lost over the shins. Pallesthesia, two point discrimination and sense of position were markedly diminished. There was spastic paraplegia in extension of the lower extremities, and the patient was unable to walk. The Queckenstedt test showed complete block, which was shown by roentgenograms taken after injection of iodized poppyseed oil to be at the second thoracic level.

At operation, on October 3, a fusiform mass of tough tissue was observed to lie extradurally and to extend from the fifth cervical to the third thoracic level. Its greatest thickness was at the first and second thoracic level. Most of the tissue was removed, with marked decompression of the cord. The lesion proved to be inflammatory and was related to obscure osteomyelitis of the spine.

A sweating test done on October 2, before operation, showed good sweating above the third dorsal segment and markedly reduced sweating from the third to the seventh dorsal segment. There was a definite level at the seventh dorsal segment below which there was complete absence of sweating.

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19. Ascroft, P. B.: The Basis of Treatment of Vasospastic States of the Extremities: An Experimental Analysis in Monkeys, Brit. J. Surg. **24**:787-816, 1937.

Course.—One month after operation sensation had returned to an almost normal degree. Motor function had returned rapidly, and the patient was walking with crutches.

A sweating test on October 25, repeated under the same conditions as those in the first test, showed moderate to good sweating down to and including the toes, which was equal on the two sides.

Conclusion.—Sweat fibers may be physiologically blocked by a compressing lesion of the cord and recover function in a relatively short time, concomitant with recovery of other tracts.

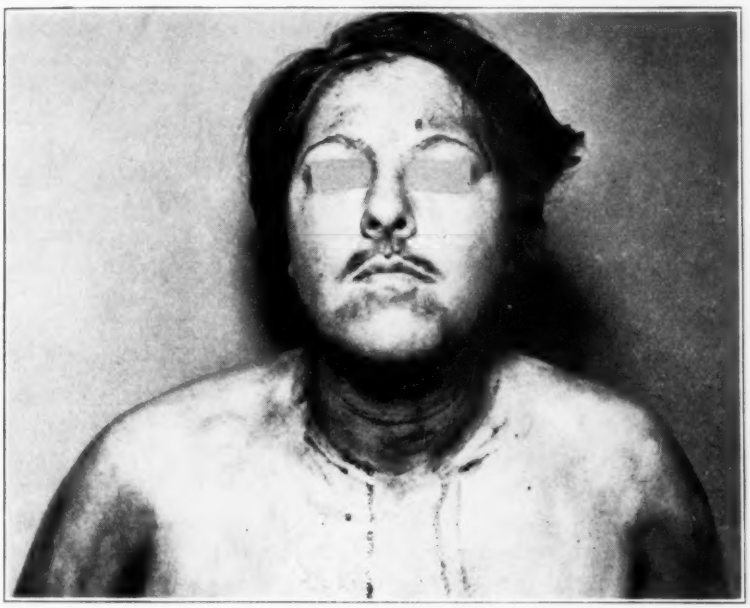

Fig. 12 (M. H., case 22).—Thermoregulatory sweating test ninety-eight days after triple ligation of the left common carotid artery below its bifurcation. There is no difference in sweating on the two sides of the face.

Case 19 (M. P.).—A white woman aged 29 had had Pott's disease of the cervical portion of the spine since the age of 16. A roentgenogram revealed marked collapse of the cervical portion of the spine with pronounced calcification. Examination revealed complete paraplegia in flexion of the lower extremities, with hyperactive deep reflexes, a positive Babinski sign and rapid ankle clonus of small amplitude. The upper extremities were essentially normal except for some atrophy of the intrinsic muscles of the hands. Sensation of pain and temperature was lost below the umbilicus and was preserved above. Sensibility for position and touch over the lower extremities was about 75 per cent normal.

A sweating test, on Dec. 2, 1939, showed a sharp level at the umbilicus above which sweating was normal and below which it was entirely abolished.

Inference.—Since there was clinical evidence that the posterior columns were largely intact but sweating was absent below the umbilicus, it is inferred that the posterior columns contain no sweat fibers.

CASE 20 (G. H.).—A white girl aged 19 had fracture of the fifth and sixth thoracic vertebrae with a complete transverse lesion of the cord at the sixth thoracic level on Feb. 1, 1940. A sweating test under a heat cradle on February 26 revealed abundant sweating to the level of the umbilicus (tenth dorsal segment) and complete absence of sweating below.

Conclusion.—The upper five anterior thoracic roots supply abundant sweat fibers down to the tenth dorsal segment.

CASE 21 (I. F.).—A white woman of 52 was admitted on Aug. 11, 1939 with complete transverse myelitis at the eighth cervical segment.

A sweating test on August 24 revealed complete absence of sweating over the entire body.

EFFECT ON SWEATING OF LIGATION OF A COMMON CAROTID ARTERY

CASE 22 (M. H.).—A white woman of 28 had traumatic arteriovenous aneurysm on the left side, probably at the cavernous sinus. Because of intolerable roaring noises in the head, the left common carotid artery was ligated. On Jan. 24, 1939 the artery was ligated tightly with silk in three places. The operation was followed by no untoward result, and the roaring ceased.

A sweating test, on May 2, 1939, revealed no detectable departure from normal sweating and no difference on the two sides of the face (fig. 12).

Conclusion.—No sweat fibers course with the common carotid artery. (Regeneration was possible, but not likely.)

CONCLUSIONS

1. In a sympathectomized zone, sweating will occur on two surfaces of the skin which are in contact, such as in the axilla or the antecubital fossa if the forearm is flexed. We believe that this is a manifestation of activity of denervated sweat glands.

2. Section of the upper five anterior thoracic roots bilaterally causes almost complete anhidrosis of the face and hyphidrosis down to the second dorsal segment, usually with retention of fair thermoregulatory sweating of the neck and normal sweating over the remainder of the body.

3. The anterior roots of the second thoracic nerve subserve abundant sweating of the head and upper extremities and of the trunk down to the level of the sixth dorsal segment (1 case). Section of anterior roots from the third to the ninth thoracic, inclusive, does not noticeably diminish sweating.

4. The sweat fibers in any anterior root are distributed to at least four or five sympathetic ganglia. Our results agree roughly, but not

entirely, with those in Foerster's table. If one utilizes sudomotor, pilomotor and vasomotor tests and signs in the diagnosis of the level of lesions of the cord, one should take into account the fact that a demonstrable level on the skin does not necessarily correspond with the segment of the cord representing that somatic dermatome.

5. Anterior rhizotomy alone for purposes of sympathectomy is impractical. The number of roots that would have to be sectioned to be effective is greatly out of proportion to any possible advantage. Also, extensive rhizotomy is fraught with the danger of ischemia of the cord.

6. No sweat fibers reside in the posterior thoracic roots or in the sheath of the common carotid arteries.

7. Complete sections of the anterior and anterolateral columns of the cord do not diminish sweating unless the result is complicated by evident injury to the pyramidal tract, indicating proximity of the section to the latter. Probably no sweat fibers reside in the posterior columns.

8. From our studies we agree that the autonomic tracts subserving sweating are situated just anterior and close to the pyramidal tracts. Some sweat fibers may possibly reside in the pyramidal tracts.

9. Complete transverse myelitis at the eighth cervical segment completely abolishes thermoregulatory sweating.

10. Sweat fibers, and therefore probably all autonomic fibers, may be physiologically blocked by a lesion of the cord and recover function concomitantly with recovery of other tracts in the cord, particularly the pyramidal tracts.

11. The sweating test may serve as an aid in the differentiation of disease of the anterior horn cells from involvement of peripheral nerves, and as an aid to prognosis of recovery of the spinal cord. The degree of return of thermoregulatory sweating from time to time offers some measure of the viability of the cord.

12. When sweating is abolished over a large proportion of the body surface, the normally sweating zone appears to be overactive. We believe this is compensatory activity, necessary for the proper maintenance of body temperature.

13. After cervicodorsal ganglionectomy we have found no evidence for regeneration of sympathetic fibers by the thermoregulatory and pilocarpine sweating tests up to twenty months. After lumbar ganglionectomy no evidence for regeneration has been obtained by the thermoregulatory sweating test up to eight months.

NEOPLASM OF THE POSTERIOR FOSSA SIMULATING CEREBRAL VASCULAR DISEASE

REPORT OF FIVE CASES WITH REFERENCE TO THE ROLE OF THE MEDULLA IN THE PRODUCTION OF ARTERIAL HYPERTENSION

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The purpose of this communication is to present 5 cases in which the diagnosis of tumor of the brain was made either shortly before death or at necropsy. An attempt will be made to reconstruct in retrospect the sources of errors committed in each case.

REPORT OF CASES

CASE 1.—*A man aged 58 had headache, dysphagia and weakness following an attack of bronchitis. Temporary improvement was followed by an exacerbation of symptoms. Signs of bilateral involvement of the pyramidal tracts, cerebellum and bulb were noted. The clinical diagnosis was multiple sclerosis, pseudobulbar palsy or vascular disease of the pons. At necropsy a tumor of the cerebellopontile angle was found.*

The past and family histories were of no significance. In February 1927, about one and one-half years before the patient's admission to the neurologic division of the Montefiore Hospital, after an attack of bronchitis, there developed severe headache, difficulty in swallowing and generalized weakness and asymmetry of the face, which was drawn to the right side. Two months later he fell suddenly, but suffered no ill effects. At about this time there was noted improvement in his previous complaints. His face straightened out, and swallowing became less troublesome. A month later his general weakness recurred, and he was admitted to a hospital, where a diagnosis of thrombosis of the right posterior inferior cerebellar artery was made. Thereafter he had difficulty in maintaining his balance, was often dizzy and fell frequently. Weakness first of the left and later of the right arm followed, and then difficulty in starting micturition. About March 1928 the dysphagia recurred, and shortly thereafter dysarthria was noted. On examination in the neurologic division of the Montefiore Hospital, in July 1928, the patient appeared older than his stated age. The blood pressure was 110 systolic and 70 diastolic. There was evidence of chronic bronchitis. Examination of the heart revealed no abnormalities. Neurologic examination disclosed: intention tremor and ataxia in the finger to finger, finger to nose and heel to knee tests bilaterally,

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more marked on the right; bilateral signs of involvement of the pyramidal tracts and paresis of the four extremities; questionable hypalgesia and hypothermesthesia over the left side of the body; normal fundi oculorum; inequality of the pupils, the right being larger than the left; bilateral corneal analgesia and diminished pain and temperature sensations over both sides of the face, with questionable involvement of tactile sensibility, and deviation of the jaw to the right. Spontaneous vertical and horizontal nystagmus was noted; there was no impairment of the ocular movements. The face was slightly flattened on the right side, and hearing was slightly diminished on the left. The uvula deviated to the left, and there was

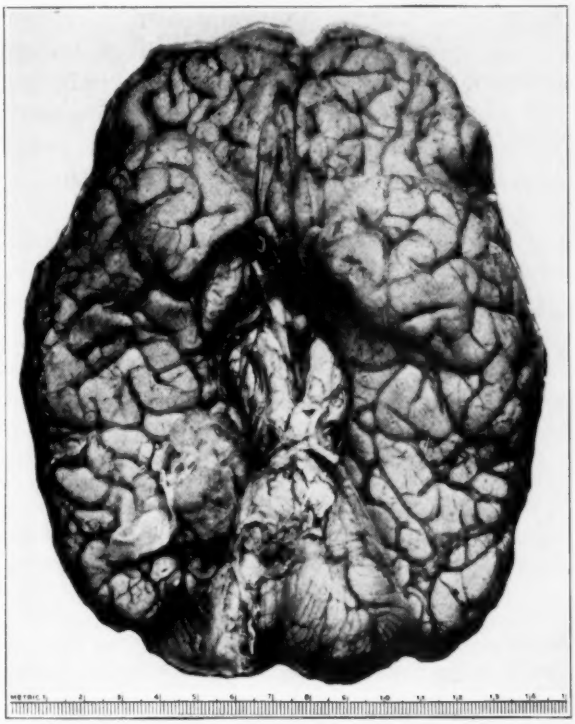

Fig. 1 (case 1).—Gross specimen of the brain, showing location of the acoustic perineurial fibroblastoma.

dysarthria suggestive of scanning speech. There was a mild tension defect, but the mental condition was otherwise intact. Vestibular tests revealed no abnormality. There was no record of spinal puncture. The neurologic status remained unchanged, and two and one-half months after admission the patient suddenly died.

General necropsy findings were bronchopneumonia, accessory spleen, slight atherosclerosis of the coronary vessels and moderate atherosclerosis of the aorta. Examination of the brain (fig. 1) revealed a perineurial fibroblastoma of the right cerebellopontile angle. This had pushed the pons and cerebellum to the left, causing distortion and herniation of the bulb and of part of the cerebellum into the foramen magnum and traction on the right cerebral peduncle.

Two features of this case served to obscure the correct diagnosis. The first was the sudden onset, remission and exacerbation of symptoms. It is to be noted, however, that the course of cerebral neoplasm is not always characterized by a gradual and progressive appearance of symptoms. In a number of reported instances the onset has been so sudden that the clinical impression was one of apoplexy. It is similarly true that the signs and symptoms of tumor of the brain may disappear, giving a picture of remission. Such events must be caused by temporary circulatory disturbance in the brain resulting from pressure of a tumor on the blood vessels. That compensation for this embarrassment may later occur is likely, and under such circumstances the clinical impression will be that of a remission of symptoms. The second feature which confused the picture was the impression of dissemination of lesions because of the signs of bilateral involvement of the pyramidal tracts and cerebellum, as well as the signs of scattered lesions in the bulb. It will be recalled that tumors of the posterior fossa encroaching on the brain stem in an already cramped space are capable of producing severe distortion, particularly when the bulb is being driven into the foramen magnum. This produces elongation of the peduncles with consequent bilateral pyramidal tract signs, in addition to the signs produced by local pressure, thus giving rise to a picture of dissemination. In an older person with evidence of cardiovascular disease, such dissemination is ascribed to diffuse vascular disease; in a younger person it is generally thought to be indicative of multiple sclerosis. In the case just cited both diagnoses were considered.

In the following case a still more difficult problem is presented, namely, the coexistence of cardiorespiratory disease and tumor of the brain.

CASE 2.—*A man aged 55 had six admissions to the hospital for recurrent anginal attacks and acute pulmonary edema, associated with dizziness, weakness and hypertension. He was treated repeatedly for bizarre attacks of respiratory distress until the late development of amblyopia called attention to intracranial disease. He died before operation could be attempted. Tumor of the eighth nerve and arteriosclerosis were observed at necropsy.*

A man aged 55 was first admitted to the medical service of the Montefiore Hospital in December 1933. He had suffered for a year from spells of weakness, dyspnea, dizziness and hypertension. Anginal seizures had occurred for three weeks. Examination revealed obesity, cyanosis, edema of the legs, pulmonary emphysema and a blood pressure of 170 systolic and 100 diastolic. He was treated with theobromine and discharged in one and one-half months. A month later he was readmitted with acute pulmonary edema. His blood pressure varied within a few hours from 230 systolic and 120 diastolic to 165 systolic and 125 diastolic. He was treated for congestive heart failure and discharged. He had also complained of weakness in walking, which continued until his third admission nine months later, when he again presented the picture of acute pulmonary edema. Examination of the ears at that time showed some diminution in hearing on the

right. Noteworthy was the apparent ease with which these attacks could be terminated on the application of tourniquets to the extremities. He was discharged and stayed home for about one month. On his fourth admission, in addition to his previous complaints, he stated that all his extremities felt "dead." One examiner expressed the opinion that the attacks were "mainly mental" in origin. The patient's heart at this time was enlarged. He was admitted for the fifth time three months after the previous discharge with the added complaint of pain in the left supraorbital region, of five weeks' duration. He also complained of some diminution of vision. Examination of the fundi disclosed papilledema and "hemorrhagic neuroretinitis," which was diagnosed as "myocardial and nephritic neuroretinopathy." The blood pressure at this time was 186 systolic and 110 diastolic. He received instant relief from Cheyne-Stokes respiration by even the loosest application of tourniquets about his wrists. He continued to complain of headache and amblyopia but was discharged on Jan. 1, 1936. Five months later he was admitted for the sixth and last time, with papilledema of 6 D., left-sided headache and dizziness. The blood pressure on admission was 186 systolic and 110 diastolic. A few days later it was 135 systolic and 95 diastolic. A Bárány examination revealed abnormal responses on the right side. Neurologic examination at this time disclosed: staggering gait, with a tendency to fall to the right; hyperactive deep reflexes in the left lower extremity; poor plantar response on the right; nystagmus on right lateral gaze; right corneal hypalgesia, with diminution of pain, touch and temperature sensation over the second and third divisions of the right fifth nerve; perversion of taste on the right side of the tongue, and diminution of nerve conduction in the left ear. There was some past pointing to the right with the left hand. A spinal puncture revealed an initial pressure of 260 mm., an Ayala index of 4.6 and 127 mg. of protein per hundred cubic centimeters. Ventriculograms revealed no air in the fourth ventricle, and the third and lateral ventricles were markedly dilated. An operation for neoplasm of the posterior fossa was attempted but had to be abandoned, owing to the patient's poor general condition. He died three and one-half years after his first admission.

Necropsy revealed pneumonia, arteriosclerosis of the coronary vessels, moderate hypertrophy of the heart (left ventricle) and renal arteriolosclerosis. Examination of the brain (fig. 2) disclosed diffuse and marked atherosclerosis. Lying in the right cerebellopontile angle was an acoustic perineurial fibroblastoma, measuring 3.5 by 3.5 cm., which compressed the pons and cerebellum. The cerebral hemispheres appeared normal.

Factors obscuring the diagnosis here were the severe cardiorespiratory complaints, which far overshadowed the neurologic picture. The question arises, however, whether these attacks can be explained entirely on the basis of the existing nephrosclerosis and arteriosclerotic heart disease. It is noteworthy that the bouts of dyspnea were bizarre and unlike those commonly encountered with paroxysmal pulmonary edema. They were strikingly brief and were easily terminated by the loose application of tourniquets, so that it was thought that the attacks were "mainly mental." It is possible that they were related to the presence of a tumor of the posterior fossa which compressed the pons and medulla, thus exerting effects either on "centers" or on descending pathways presiding over the regulation of cardiorespiratory function. The occur-

rence of Cheyne-Stokes breathing can be explained as readily by medullary compression as by hypertensive heart disease. Straub and Meier [1] expressed the belief that local changes in the bulb, producing asphyxia of the respiratory center through either spasm or sclerosis, may be the cause of what they called "cerebral dyspnea." Cushing [2] described alterations in the pulse as well as respiratory difficulties, including Cheyne-Stokes respiration, in several of the cases of tumor of the eighth nerve cited in his monograph. These symptoms were associated with

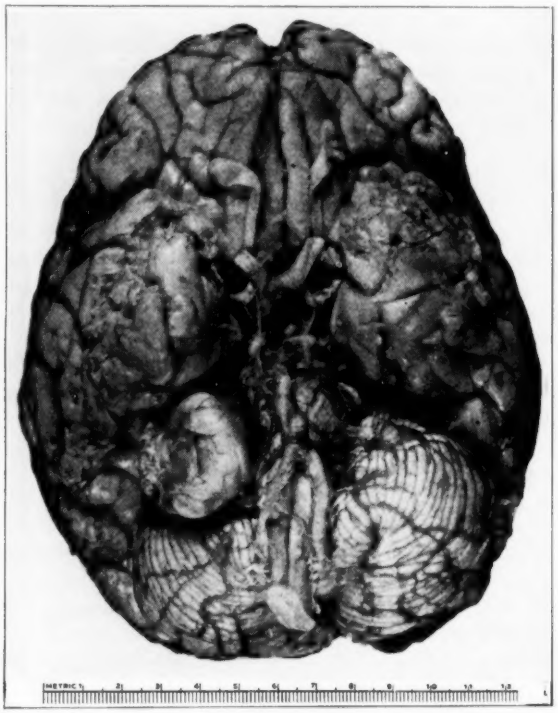

Fig. 2 (case 2).—Gross specimen of the brain, showing location of the acoustic perineurial fibroblastoma.

so-called cerebellar fits and were interpreted by him as of medullary origin. Whether these alterations in regulation of breathing are to be explained by direct pressure on the medulla or on the regional blood vessels cannot be stated. The important fact seems to be that symp-

1. Straub, H., and Meier, K.: Blutreaktion und Dyspnae bei Nierenkranken, Deutsches Arch. f. klin. Med. **138**:208, 1922.

2. Cushing, H.: Tumors of the Nervus Acusticus, Philadelphia, W. B. Saunders Company, 1917, p. 174.

toms commonly attributed to cardiovascular disease may be caused by changes occurring in the region of the so-called respiratory center in the brain stem. This possibility should, therefore, be borne in mind, particularly when there are atypical features in the cardiorespiratory symptoms, such as were obtained in this case. Of equal interest was the profound variability of the arterial tension. The latter displayed a marked rise, from 165 systolic and 125 diastolic to 230 systolic and 120 diastolic, within the space of a few hours; on another occasion it measured 135 systolic and 95 diastolic. There was no apparent explanation for these changes. The possible relationship between local medullary changes and vasomotor phenomena will be discussed later.

CASE 3.—*A man aged 56 with arterial hypertension presented a history of "stroke," followed by reduction in hearing, weakness of the right side of the face and left hemiparesis. Progressive weakness, headache and vertigo supervened. He died suddenly. A right "acoustic neuroma" was revealed at necropsy.*

A man aged 56 was admitted to the neurologic division of the Montefiore Hospital with a history of a "stroke" four and one-half years before admission. No further details were known save that he recovered, with retention of diminished hearing and weakness of the right side of the face and the left side of the body. He was treated for hypertension. There were no new complaints until four and one-half months before admission, when he awoke one night at 2 a. m. complaining of severe headache, which persisted to the date of his admission. Dizziness, ataxia and progressive generalized weakness followed. Later he became hoarse and had urinary retention and diminution in vision. There was occasional projectile vomiting. Examination revealed the presence of hypertensive and arteriosclerotic heart disease, with a blood pressure of 190 systolic and 120 diastolic, an enlarged heart, generalized arteriosclerosis, pulmonary emphysema and an enlarged prostate. Neurologic examination revealed clouding of the sensorium; bilateral ataxia in the finger to nose test, more marked on the right, with defective associated movements and a tendency to the cogwheel phenomenon in both upper extremities, especially in the right; spastic paraparesis, with some weakness in the right upper extremity and generalized hyperreflexia, more marked on the right; tonic plantar response on the right, with a tendency to grasping and sucking reflexes on the same side; fine nystagmus on left lateral gaze, weakness of the right facial nerve of supranuclear type; depressed gag reflex, and paralysis of the right vocal cord. One observer noted corneal hypalgesia on the right and facial weakness of the lower motor neuron type on that side. Hearing was diminished on the right, for both air and bone conduction. The fundi were normal. Lumbar puncture revealed an initial pressure of 125 mm. of water, with evidence of partial block. After manipulation of the jugular veins the pressure rose to 180 mm. of water. This was attributed to the patient's lack of cooperation. The protein of the spinal fluid measured 68.2 mg. per hundred cubic centimeters. Roentgenograms of the skull revealed areas of bone absorption in the parietal and temporal regions, with some frontal hyperostosis. After catheterization the blood pressure fell from 190 systolic and 120 diastolic to 130 systolic and 90 diastolic. Progressive stupor was noted. On the day before death a sudden episode of unconsciousness occurred, during which the head turned to the left, the blood pressure fell and the pulse quickened. On the day of death

the urea nitrogen of the blood measured 30 mg. per hundred cubic centimeters. Pulmonary edema developed and the patient died. The clinical diagnosis was vascular encephalopathy.

Necropsy revealed nephrosclerosis, slight hypertrophy of the heart, benign adenomatous hyperplasia and hypertrophy of the prostate, hemorrhagic cystitis and acute dilatation of the stomach. Except for rare atheromatous plaques, the aorta was normal. There was aspiration pneumonia. The brain (fig. 3) showed mild arteriosclerosis. A typical perineurial fibroblastoma of the eighth nerve was noted

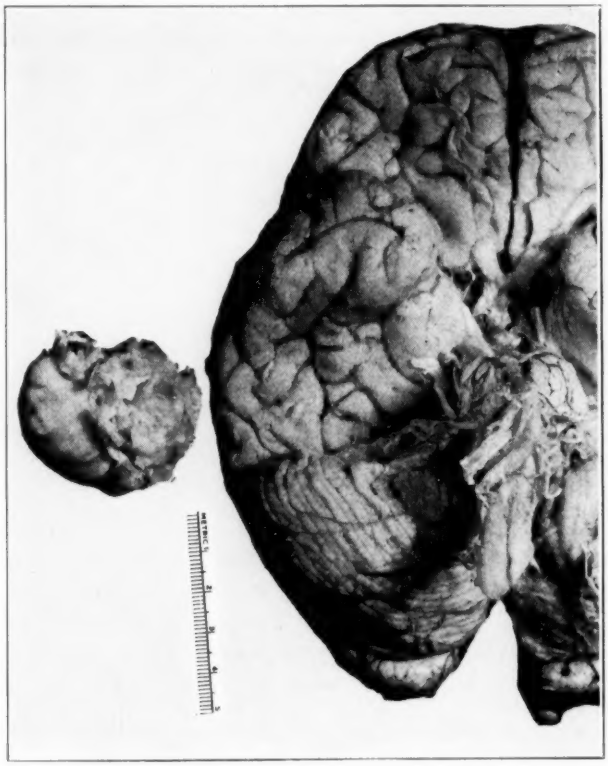

Fig. 3 (case 3).—Gross specimen of the brain, showing arteriosclerosis and the acoustic perineurial fibroblastoma removed from its bed.

in the right cerebellopontile angle. The tumor compressed the right peduncle, substantia nigra, pons and medulla. The right cerebellar hemisphere was larger than the left and was compressed and elongated. The cerebral aqueduct and superior ventricular system were dilated.

The striking feature of this case was the apoplectiform onset with partial recovery and later exacerbation associated with signs fairly typical of an "acoustic neuroma." The clinical picture was one of dissemination: In addition to the signs of tumor in the cerebellopontile angle,

there were grasping and sucking reflexes, tonic foot responses, extrapyramidal rigidity and clouding of the sensorium. A third feature which served to obscure the diagnosis was the presence of arterial hypertension and other signs referable to the cardiovascular system, which made it reasonable to explain all the symptoms on a vascular basis. Although the ventricular system was seen to be dilated at necropsy, there was neither increase of cerebrospinal fluid pressure nor papilledema. Presumably the tumor caused the partial manometric block, which therefore masked the existence of intracranial hypertension.

CASE 4.—*A man aged 52 had headache and progressive paralysis of the face, arm and leg on the right after an attack of influenza. Later there were signs of bulbar disturbance and occasional episodes of coma. He died of bronchopneumonia. A meningioma of the middle and posterior fossae was observed at necropsy.*

A man aged 52 was admitted to the neurologic division of the Montefiore Hospital in May 1938 with the following history: In March 1932 he had an attack of influenza associated with fever and lethargy, of one week's duration. Thereafter he was easily fatigued, slept much of the time and complained of headache. Three months later drooping of the right side of his face was noted, followed by complaint of heaviness and weakness of the right arm and, later, of the right leg. He was admitted to a hospital in New York, where the diagnosis was one of "probable encephalitis; possible neoplasm." Three years later, at another hospital, a diagnosis of "old hemiplegia" was made. Since that time the patient had not been able to walk, speech became unintelligible and dysphagia, pathologic laughing and crying and intellectual deterioration developed. There were transient episodes of coma. Examination at the Montefiore Hospital revealed a blood pressure of 160 systolic and 98 diastolic, but no abnormality of the heart or lungs. The neurologic findings were: pathologic laughing and crying; right spastic hemiplegia, generalized hyperreflexia, exhaustible abdominal reflexes, a Babinski sign on the right and bilateral Hoffmann signs; inequality of the pupils, the right being larger than the left, and poor pupillary reaction to light or on attemps at near vision; difficulty in upward, downward and extreme lateral gaze bilaterally; weakness of the right facial nerve of central type; bilateral diminution of hearing, with normal air and bone conduction formulas; diminution of the pharyngeal reflex and almost no movement of the uvula, and bilateral atrophy of the tongue and weakness in protruding it. Lumbar puncture yielded fluid under an initial pressure of 100 mm. of water, with a protein content of 51 mg. per hundred cubic centimeters. A roentgenogram of the skull was normal. The ophthalmologist reported slight indentation of the veins by the arterioles, but no other abnormalities. Encephalographic study was advised, but the patient suddenly died of aspiration pneumonia.

Necropsy revealed bronchopneumonia, slight tubular bronchiectasis, dilatation of of the heart and mild atherosclerosis. The brain (fig. 4) presented cortical atrophy, especially in the frontal regions, and a large meningeal fibroblastoma occupying the left middle and posterior fossae, the tumor being attached to the anterior border of the tentorium just to the left of the incisura. It lay between the left hippocampus and the peduncle, stretching the latter to a thin, ribbon-like structure and displacing it to the right. The tumor pushed the temporal lobe to the left and the mamillary bodies and mesencephalon to the right and extended downward to the pons, compressing it as well as the left fifth and seventh cranial nerves. The tumor measured about 2.5 by 2.5 cm. and appeared to be enucleable. Histologic exami-

nation of the brain disclosed demyelination of the left inferior portion of the thalamus, as well as destructive changes in the substantia nigra, corpus Luysi, hypothalamus and mamillary body on the left. In sections farther caudad destructive changes were noted in about one-half the left side of the pons. There was distortion of the greater part of the left side of the mesencephalon.

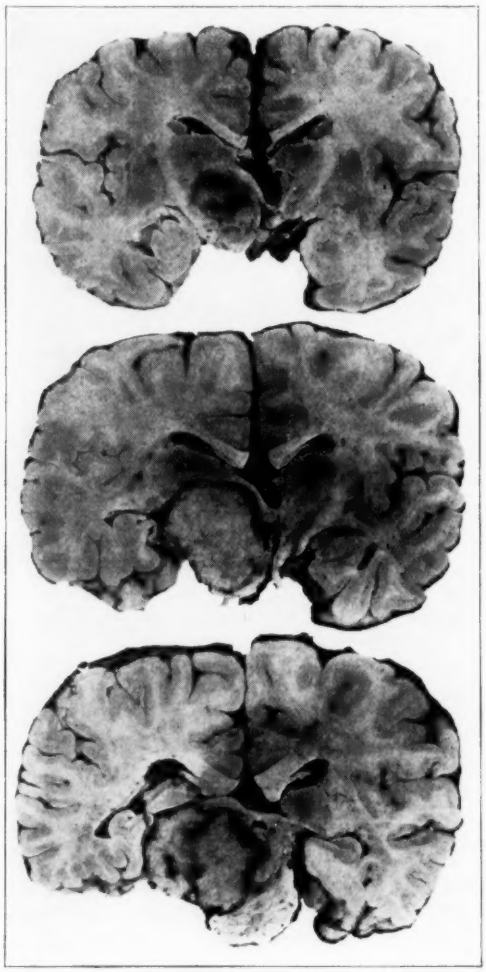

Fig. 4 (case 4).—Sections of the brain, showing a meningeal fibroblastoma attached to the anterior portion of the tentorium, compressing the pons and peduncle from the left.

This is another case in which the condition was characterized by an acute onset and coexisting arterial hypertension. Despite the lethargy and consequent clinical impression of encephalitis, the gradual and pro-

gressive "march" in the development of the pareses speaks against either an inflammatory or a vascular origin. Another difficulty in reaching the correct diagnosis was due to the apparent dissemination of neurologic signs, although the location of the tumor explains them adequately. As in the previous cases, the occurrence of vascular hypertension served to promote the impression of vascular encephalopathy.

CASE 5.—*A man aged 66 with hypertension had progressive difficulty in walking, followed by headache, ocular palsies and mental deterioration. At four different hospitals a diagnosis of cerebrovascular disease was made. Death followed craniotomy. A hemangioma of the cerebellum was found.*

A man aged 66 was admitted to the Rockland State Hospital through commitment from Bellevue Hospital on Sept. 27, 1939.[3] Progressive weakness had been noted since June 1939. By the middle of that month the patient complained of severe headaches, especially on lying down; his right eye began to turn outward, and his voice became hoarse. There followed mental confusion and urinary and fecal incontinence. Between that time and his entrance to the Rockland State Hospital he was admitted successively to three hospitals, in each of which the diagnosis of cerebral arteriosclerosis was made. Examination at the Rockland State Hospital revealed a blood pressure of 160 systolic and 100 diastolic, cardiac enlargement, rales at the bases of both lungs and a questionably palpable liver. The patient was torpid and uncooperative and complained of headaches. Neurologic examination disclosed severe ataxia on standing with a tendency to fall backward, right hemiparesis associated with hypotonia and hyperreflexia, ankle clonus and Oppenheim and Hoffmann signs on the right; bilateral grasping and sucking reflexes, and absence of the right abdominal reflexes. The right arm drifted outward. Examination of the fundi revealed bilateral spokelike hemorrhages radiating from the disk but no measurable papilledema, although the margins of the disks were obscured. The sixth nerves were paretic, especially the right, but the patient would not cooperate in tests for diplopia. Both corneal reflexes were diminished. Weakness of the right side of the face of upper motor neuron type was present. The voice was hoarse, but no weakness of either vocal cord was demonstrable; the palate was pulled strongly to the left on phonation. Some aphasia was present, but the patient's mental state did not permit a detailed study. He was confused and distractible and tended to perseverate. Examination of the spinal fluid revealed a protein content of 70 mg. per hundred cubic centimeters; the fluid was under increased pressure, which fell markedly after removal of 10 cc. A roentgenogram of the skull showed a hazy shadow involving the posterior two thirds of the sella turcica, with destruction of the posterior clinoid processes and dorsum sellae. Some irregular shadows were also noted in the posterior fossa. During his further stay at the Rockland State Hospital, the patient appeared more lucid after spinal punctures. He yawned and hiccuped excessively. There was a suggestion of bitemporal homonymous hemianopia. A clinical diagnosis of tumor of the brain was made, and the patient was returned to Bellevue Hospital for surgical intervention. Ventriculographic examination performed there revealed symmetric hydrocephalus extending down to the middle of the aqueduct, with no air in the fourth ventricle. A suboccipital craniotomy was performed. A blue tumor mass,

3. This case is reported with the permission of Dr. R. E. Blaisdell, Superintendent, Rockland State Hospital, and Dr. Karl Bowman, Director of the Psychiatric Division, Bellevue Hospital.

measuring 2 by 1.5 inches (5 by 3.8 cm.) and occupying most of the cerebellum, was removed. After operation the temperature rose to 105 F., and the patient died six hours later. On microscopic examination the tumor proved to be a hemangioblastoma.

In retrospect, the last case does not offer the diagnostic difficulties present in the first four. Nevertheless, the patient was sent from hospital to hospital over a period of months, while he became progressively worse. The combination of impending senility, obvious cardiorespiratory disease and hypertension served to discourage a careful anamnesis or a painstaking clinical examination. The diagnosis of cerebral arteriosclerosis should be restricted to those cases in which ophthalmoscopic study, palpation of the peripheral vessels or other direct examination of the cardiovascular-renal system reveals unquestionable arteriosclerosis or arteriolosclerosis. Even under such circumstances, however, a careful history should be obtained. Vascular disease does not usually produce a progressive "march" of symptoms, nor is there any guarantee that a person harboring vascular disease is immune from cerebral neoplasm.

COMMENT

Four of the 5 patients whose cases are reported presented evidences of arterial hypertension, which in 2 instances was markedly labile. This finding raises the question of the possible relationship between intracranial disease and arterial tension. Abbott and his associates [4] reported a case of a woman aged 48 with hypertension who was subjected to two subtotal adrenalectomies because it was believed that the jacksonian fits from which she suffered were hypertensive in origin. Finally, after air studies were completed, a craniotomy was performed and a meningioma revealed. In his monograph on the carotid sinus and the cerebral circulation, Ask-Upmark [5] reviewed 486 cases of verified tumor of the brain in patients ranging in age from 20 to 44 years who were operated on by Cushing from 1914 to 1932. In the group taken as a whole, the incidence of arterial hypotension (systolic pressure equal to or less than 100 mm. of mercury) was 20 per cent and that of hypertension (diastolic pressure equal to or greater than 100 mm. of mercury) was 4 per cent. With the group divided on the basis of supratentorial and infratentorial tumors, the incidences of hypertension were 1.3 and 9 per cent respectively. Much higher percentages for the incidence of high blood pressure were obtained in cases of acoustic tumors in the higher age groups. Thus, of 64 cases of acoustic tumors occurring in persons from 45 to 65 years of age, the diastolic pressure in 33 per cent was equal to or

4. Abbott, W. D.; Anderson, E. W.; Van Epps, C., and Walker, A. E.: Hypertension and Brain Tumor: Case Report, J. Iowa M. Soc. **26**:303, 1936.

5. Ask-Upmark, E.: The Carotid Sinus and the Cerebral Circulation, Acta psychiat. et neurol., 1935, supp. 6, p. 1.

greater than 100 mm. of mercury, whereas in 50 per cent the diastolic pressure was equal to or greater than 90 mm. In a small group (11 cases) of verified acoustic tumors from the Montefiore Hospital, a diastolic pressure of 90 mm. or higher was found in 5 cases (45 per cent). There seems, therefore, to exist some relationship between arterial hypertension and tumors located in the posterior fossa. In the opinion of Ask-Upmark, the explanation is to be found in the so-called Cushing mechanism — involvement of the vasomotor centers of the medulla through local compression.[6] Fishberg[7] failed to find adequate evidence that essential hypertension is associated with organic changes in the vasomotor center or its blood vessels but expressed the belief that there is adequate evidence that organic lesions of the central nervous system can produce elevation of blood pressure. Three cases of anterior poliomyelitis were cited by Salus,[8] in which arterial hypertension developed in the course of the disease parallel with the appearance of bulbar signs. In 2 nonfatal cases there occurred recession of the hypertension as the bulbar signs cleared. A similar example was cited by Nordmann and Müller,[9] who described a case of poliomyelitis in which progressively increasing hypertension developed to values as high as 209 systolic and 140 diastolic. In this instance death occurred through respiratory paralysis. Necropsy revealed a medullary lesion in the substantia reticularis grisea, in which the authors postulated the existence of a vasomotor center. They did not discuss the question whether the lesion was a destructive or an irritative one. In reviewing his 3 cases, Salus considered the possibility that descending pathways mediating vasomotor impulses, rather than so-called centers, may be involved.

I have reviewed 82 cases of amyotrophic lateral sclerosis from the Montefiore Hospital from the standpoint of determinations of blood pressure. In this series, 9 patients were under 40 years of age, and 6 of them (66 per cent) were found to have a diastolic pressure equal to or greater than 100 mm. of mercury. All of these patients had unmistakable clinical evidence of bulbar involvement, as did 1 of the 3 not presenting hypertension. Furthermore, in the group as a whole there was an abnormally high incidence of hypertension, but the occurrence of hypertension in the younger patients is considered more suggestive,

6. Cushing, H.: Some Experimental and Clinical Observations Concerning States of Increased Intracranial Tension, Am. J. M. Sc. **124**:375, 1902.

7. Fishberg, A. M.: Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1930.

8. Salus, F.: Zur Frage des bulbären Hochdruckes, Klin. Wchnschr. **11**:1542, 1932.

9. Nordmann, M., and Müller, O.: Ueber die Lage eines Blutdruckregulierenden Zentrums in der Medulla oblongata, Klin. Wchnschr. **11**:1371, 1932.

since they do not ordinarily fall into the age group in which arterial hypertension is common in the general population. Apparently, lesions in the posterior fossa are in some way related to arterial hypertension, although the precise nature of this relationship has not been established. Of importance, however, is the fact that expanding growths in this region seem to be capable of producing high blood pressure. This finding demands additional caution in the interpretation of cerebral signs and symptoms in persons with hypertension and should make one hesitant about attributing neurologic phenomena to so-called hypertensive encephalopathy or vascular encephalopathy.

Even when the onset of symptoms is apoplectiform a neoplasm is not ruled out. The cases cited reveal that the earliest symptoms of tumor of the brain may be typical of a "stroke," and under those circumstances only the subsequent course of the illness will clarify the diagnosis. When after an ictus there occurs progressive development of symptoms, the diagnosis of vascular accident is untenable and the presence of an expanding growth must be suspected. Under such circumstances the "stroke" is likely to be a vascular phenomenon, but secondary to pressure effects produced by the tumor itself. As previously noted, only a painstaking anamnesis will separate this group from the large one of chronic vascular disease which abounds in hospitals for the chronically ill and in the state institutions.

SUMMARY

1. Five cases of tumor of the brain are described in which the diagnoses were made either at necropsy or shortly before death. In each case the working diagnosis had not been that of intracranial neoplasm. The source of error in each instance is discussed. In 4 cases arterial hypertension was present. Evidence is submitted that hypertension may be a symptom of disease within the posterior fossa. In 1 instance paroxysmal respiratory difficulties were also present; the relation of pressure on the medulla to such disturbances is discussed.

2. Attention is drawn to the fact that initial symptoms of tumor of the brain may either be apoplectiform or be followed by an apparent remission.

3. The importance of obtaining a careful anamnesis in all cases of so-called cerebrovascular disease or hypertensive encephalopathy is stressed. Because the usual age period of these conditions coincides with that for tumor of the brain particular care should be exerted in the workup of such patients when they are admitted to general hospitals for the chronically ill and to state institutions.

Dr. Charles Davison, of the neuropathologic laboratories of the Montefiore Hospital, gave permission to use material from his laboratory for this publication.

METAMORPHOPSIA AND OTHER PSYCHOVISUAL DISTURBANCES IN A PATIENT WITH TUMOR OF THE BRAIN

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Psychovisual disturbances have been observed in patients with lesions of parieto-occipital zones of the nondominant cerebral hemisphere, particularly area 19 of Brodmann. Visual inattention, spatial disorientation, simultaneous agnosia, dyslexia, inability to see objects in the environment in relation to one other and to himself, metamorphopsia, macropsia, micropsia, polyopia and optic hallucinations are some of the visual abnormalities which may be found in these persons.

The following report of a case illustrates several of the many disorders which may occur in the psychovisual sphere. It is primarily with the psychologic aspects of these illusions, hallucinations and visuomotor disorders, and to a lesser extent with their anatomic correlates, that we shall be concerned in this paper.

REPORT OF A CASE

D. M., a 57 year old fruit salesman, entered the hospital because of headaches and convulsions. For one year there had been blurring of vision. Nine months prior to admission to the hospital the patient had severe headache and vomiting. At this time tonic convulsions limited to the left shoulder and the face appeared. With this there were conjugate deviation of the head and the eyes to the left, inability to speak and involuntary crying. Since then he had had spells of double vision and generalized and left-sided convulsions. On several occasions when he looked into a mirror his face appeared strange to him, and this perception was usually followed by a tonic seizure.

For three months before admission he had the impression that people were jumping toward him from the left side. On several occasions he thought he saw small people on his left. Once he had perceived images resembling figures on a cinema screen on his left side. These hallucinations were often preceded by turning of the head and eyes to the left. In addition to these disturbances there were episodes resembling petit mal seizures. When asked why he stared, he replied that the observer and not he was staring. He complained that everything about him appeared blank and that he seemed to be in a strange environment. He misidentified some persons and objects and identified others correctly but stated that they seemed very small. All these symptoms increased in severity and frequency.

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Examination.—The patient was heavy set, weighing 200 pounds (90.7 Kg.), and appeared emphysematous. The blood pressure was 120 systolic and 90 diastolic. There was no evidence of disease of the internal organs other than that of the brain.

Except for slight depression of the deep tendon reflexes on the left side, the neural status was normal. During the examination the patient was observed to have a seizure in which the head and eyes turned forcibly to the left. There were a few clonic movements of the head toward the end of the convulsion. The patient stated that during the attack he felt that some one was behind him. During the first few days in the hospital he had many similar seizures and on three occasions there were generalized convulsions with loss of consciousness. He was dull, irritable, inattentive and uncooperative throughout this period.

Course.—On the fifth day after admission to the hospital it was noted that he did not recognize objects in his left field of vision in confrontation tests. There was also slight faciobrachial paresis, and later some disturbance in the position and stereognostic senses was noted on the left. He was restless and somewhat bewildered and moaned because of headache. He complained that objects about him appeared distorted and seemed to rotate on his left side. At one time he remarked that the examiner seemed to have changed and to wear a different suit. At irregular intervals objects in his environment seemed small. He complained that a face at which he was looking grew alternately small and long.

The patient showed disorders both in the motor and in the sensory components of central visual function; the essential disorder probably was an impairment of sensorimotor coordination. In looking to the left, he reported that things appeared strange and small. Tests showed misidentification of persons and objects in the left field of vision. He could not estimate correctly the number of fingers of the examiner; he pointed past objects; he complained that a "picture had no meaning," although he was able to point to individual parts of the picture on request. In addition to the changed perceptions, which were largely confined to the left half of the field, the patient revealed physical and psychologic evidence of changed orientation in space. He could follow the finger of the examiner to the right beyond the midline only on coaxing and by special effort. When requested to read a newspaper or describe a picture, he concentrated on the details in the right half of the visual field and required the urging of the examiner before he would notice the details to the left. Examination revealed that the patient could perceive an object in the extreme periphery of the left field, but when he was presented simultaneously with two fingers, one on each side of him, and the fingers were gradually brought toward the center of vision, the finger on the left side was discerned considerably later than the finger on the right; in this way a false impression of homonymous hemianopia could be gained. This phenomenon, however, in view of the other findings, was probably a manifestation of "weakness of attention," which results from loss of associative cortical visual function rather than from a lesion of the tracts or their projection areas.[1]

Throughout the examination he made facetious remarks. When he was clear there were no definite signs of aphasia. He was able to see objects, but often they appeared meaningless to him. He had difficulty in right and left orientation.

1. Kennard (Alterations in Response to Visual Stimuli Following Lesions of Frontal Lobe in Monkeys, Arch. Neurol. & Psychiat. **41**: 1152 [June] 1939) found that after removing the visual cortex, area 8 of Brodmann, in monkeys there occurred a temporary contralateral homonymous field defect which was characterized by inability to appreciate objects.

The following are some of the patient's productions: "Lately I don't see good. I don't see what is necessary. Nothing exists before my eyes. There is nothing. Things become at times thinner and at times denser. Yesterday I looked at my doctor, and he became small. Today I feel as if the whole world is turning with me. I don't remember what I saw or said yesterday."

"I saw men and women coming from the left side. Some were small. People were going through a window on my left. Men and babies were sitting here [on the left side] and taking shaves." (The patient was clear and definite about the hallucinations.)

"What are they doing there?" The patient turned to his left. "She is handling something there. She is so big. She is moving. Now I don't see her. I saw her before. I don't know whether this is an imagination."

"They were jumping and running around on my left. I see them momentarily. Sometimes I don't see anything in the room. Everything is black, and only I am in the room. Now I am in a different room. Since you came in they put me in a different room. I see little midgets sitting there [on the left]. Those people bother me. No, they don't talk or make sounds."

"Before I saw automobile headlights on my left. Just now I see a woman and two children trying to take something from my left side. People and midgets continue to walk through the window from behind and on the left." This was annoying and disagreeable to him. Sometimes the hallucinations would disappear if the patient turned his head to the left to bring them into central vision. There was a tendency to split images, which was brought out by the fact that after the examiner had been sitting on the left the patient reported that two people had been "doing something" there. This duplication of images (cortical or monocular diplopia) was observed on several occasions.

Aphasic Status.—On examination the patient showed difficulty in counting fingers, due apparently to a distortion of visual images. The presence of a hemianopic field defect could not be established by confrontation tests, but it was observed that the patient directed his attention spontaneously to the right, especially in selective reading and picture tests. The ability to read individual letters, words and sentences was impaired. He looked at a watch, demonstrated correctly that the hands pointed to 12 and 6 but insisted that it was ten minutes after 8 o'clock. Colors were correctly named. Attempts to obey complicated commands caused difficulty and errors. Difficulties in right and left orientation seemed to be dependent on this disability. Body image disturbances were not elicited. The patient selected coins and counted money on request (1 cent; 25 cents; 27 cents) and also chose other objects as directed. In describing a picture he said, "It doesn't mean anything to me"; after some coaxing, he finally identified a ship (at the right) and later a man (at the left) but could not give the meaning of the picture. He showed difficulty in imitating the positions of fingers but named and selected individual digits correctly. His eyes were able to follow the examiner's hand to the extreme right, although sometimes there was a spontaneous tendency for them to halt at the midline. The patient seemed aware of his limitations and would remark apologetically: "Sometimes it takes me a long time to know what you want." "I am ashamed of such silly questions." He pointed past objects he tried to touch but not in a constant direction. When asked to split a line in the middle, he placed a pencil considerably below the line and insisted that he was touching it. Stereognostic and apraxic disturbances could not be demonstrated. The general attitude of the patient during the examination was cooperative, and although he seemed depressed, he occasionally made facetious remarks.

The fundi were normal. A perimetric examination revealed no gross visual field defects for recognition of motion. The pneumoencephalogram revealed deformity of the ventricular system, characteristic of a tumor in the anterior portion of the right frontoparietal and parasagittal regions. All other laboratory data were normal.

An exploratory craniotomy revealed a large infiltrating tumor in the anterosuperior portion of the right temporal lobe, extending into the parietal and frontal lobes. The patient did poorly and died on the third postoperative day.

At autopsy a huge infiltrating gliomatous tumor was observed to infiltrate the superior and anterior portion of the right cerebral hemisphere. The rest of the hemisphere was edematous. Microscopically, perivascular neoplastic infiltrations were found in the entire right hemisphere, including the occipital lobe.

COMMENT

The consistency of the type of hallucination in which figures, usually mobile and often multiple, are seen in the direction of hemianopic disturbances, with a tendency to deviation of the eyes and sometimes of the head and body in a particular direction, is suggestive of an underlying psychophysiologic process intimately associated with the normal physiology of vision. Instances of this syndrome are found in clinical observations and experimental studies. Foerster [2] described the association of hallucinations in the visual sphere as well as deviation of the eyes, the head and sometimes the entire body in cases of epilepsy and was able to produce analogous symptoms by stimulation of area 19 in the occipital lobe. Kauders [3] reported the occurrence of a visual aura in which figures of little men with knives appeared to be rushing toward the patient. Examination disclosed left hemianopic disturbances as well as deviation of the head and eyes to the left. These phenomena, which were transient, occurred in a patient with an injury to the head who subsequently recovered. Hoff and Pötzl [4] described similar hallucinations in association with a syndrome of polyopia and monocular diplopia. They maintained that the hallucinations took their origin in preserved parts of the cortex representing peripheral portions of the visual field and that the apparent wandering of the images resulted from a phasic migration of attention to these stimuli.

The parieto-occipital region, which is involved in cases of the type under consideration, is an area in which stimuli from the visual sphere appear to become integrated with proprioceptive and vestibular influences. Lesions in this region cause disturbances in the perception

2. Foerster, O., in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 6, pp. 111 and 114.

3. Kauders, O.: Drehbewegungen um die Körperlangsachse, Halluzinationen im hemianopischen Gesichtsfeld als Folge eines Schädeltraumas, Ztschr. f. d. ges. Neurol. u. Psychiat. **98**:602, 1925.

4. Hoff, H., and Pötzl, O.: Ueber Polyopie und gerichtete hemianopische Halluzinationen, Jahrb. f. Psychiat. u. Neurol. **54**:55, 1937.

of forms and the spatial order of objects and in the orientation of the patient in space (van Bogaert [5]). A dreamlike state of unreality may occur, as in the case of our patient, which favors the elaboration of faulty perceptions into complex hallucinations. When the lesion is close to the projection area of the occipital cortex the hallucinations tend to be simple and in the nature of sensory illusions, while disturbances in adjacent regions of the cortex more frequently involve generalized psychic reactions. Thus, Foerster [2] observed that perceptions of simple hallucinations occurred when he stimulated area 17 of Brodmann, but as the disorder spread to involve area 19 the hallucinations became more complex. Similarly, on prolonged stimulation of area 17 initial unformed hallucinations gradually changed into more complex hallucinations.

The occurrence of lilliputian hallucinations in our case raises the question of apparent size. Such hallucinations have been described in cases of hysteria, dreams, hypnogogic states, drug intoxications, infections and schizophrenia. Savitsky and Tarachow,[6] in their report on a case of lilliputian hallucinations during convalescence from scarlet fever, gave an extensive review of the literature. Cases of tumor of the brain in which lilliputian hallucinations occurred were reported by van Bogaert,[7] but here they were not limited to one field of vision. Leroy,[8] who made important contributions to the subject, stressed the multiplicity, mobility and brightness of color of the images. In contrast to the findings in our case, Leroy emphasized the absence of micropsia in the cases which he observed. The hallucinations which he reported were not associated with hemianopia.

SUMMARY

Phychovisual disturbances in a patient with tumor of the brain are described; the symptoms were lilliputian hallucinations, visual inattention, metamorphopsia, micropsia, macropsia and sensorimotor incoordination of the visual functions. Psychologic aspects of these visual disorders are discussed.

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5. van Bogaert, L.: Sur des changements métriques et formels de l'image visuelle dans les affections cérébrales (micropsies, macropsies, métamorphopsies, téléopsies), J. belge de neurol. et de psychiat. **34**:717, 1934.

6. Savitsky, N., and Tarachow, S.: Lilliputian Hallucinations During Convalescence from Scarlet Fever in a Child, J. Nerv. & Ment. Dis. **93**:310 (March) 1941.

7. van Bogaert, L.: Sur les hallucinations visuelles au cours des affections organiques du cerveau (Contribution à l'étude du syndrome des hallucinations lilliputiennes), Encéphale **21**:647, 1926.

8. Leroy, R.: The Syndrome of Lilliputian Hallucinations, J. Nerv. & Ment. Dis. **56**:325, 1922; The Affective States in Lilliputian Hallucinations, J. Ment. Sc. **72**:179, 1926.

CONVULSIVE SEIZURES IN DELIRIUM TREMENS

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That some patients with delirium tremens have convulsions during the course of their illness has long been known. For the most part, however, the seizures have been labeled "whisky fits," and there are few references to them in the literature. Cobb and Lennox,[1] in the chapter on epilepsy in "Oxford Medicine," remarked: "Alcohol poisoning may have epileptic seizures as a symptom," and stated that "when a relationship [of seizures to alcohol] exists, the seizure usually comes during the sobering-up process." Since in recent years much new light has been shed on the whole problem of convulsive disorders with the aid of electroencephalography and since no systematic analysis of convulsions associated with delirium tremens can be found, we thought that such a study might be timely.

ANALYSIS OF CASES

Three hundred and five cases of delirium tremens, representing 384 separate admissions to the psychiatric pavilion of the Cincinnati General Hospital between June 1, 1933 and April 1, 1940, formed the basis for this study. These were cases of active delirium tremens. We excluded all cases of acute or chronic alcoholism and cases of "impending delirium tremens." In these 384 admissions there were 32 instances of convulsions (8 per cent), while of the 305 patients who represented the 384 admissions, 29 (9 per cent) had convulsions.

These convulsions were in every case associated with the attack of delirium tremens for which the patient entered the hospital. We excluded patients with delirium tremens who had had convulsions only during previous alcoholic episodes, but not with the attack of delirium tremens for which they were admitted.

From the Psychiatric Pavilion of the Cincinnati General Hospital, and the Psychiatric Department of the University of Cincinnati.

1. Cobb, S., and Lennox, W. G.: Epilepsy, in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1939, vol. 7, pt. 2, p. 909.

Age, Sex and Color.—The ages varied from 24 to 55, the average age being 41.5 years. In 16, or over half the patients, the convulsions occurred in the decade of 40 to 49 years. Twenty-six (89 per cent) were men and 3 (11 per cent) women. Racially, 26 (89 per cent) were white and 3 (11 per cent) were Negroes. These ratios are essentially the same as those for the group without convulsions.

Family History of Convulsive Disorders.—No adequate data could be obtained on 11 of the 29 patients. Of the other 18, 16 had a family history of no significance. Only 2 patients (7 per cent) had a family history suggestive of convulsive disorder.

History of Alcoholism and Convulsions.—All the patients had a history of alcoholism of many years' duration and chiefly drank whisky. Except in 1 case, it was only after many years of drinking that convulsions began. Eighteen patients had never had a fit before

TABLE 1.—*Onset of Convulsions in Twenty-Nine Patients with Delirium Tremens*

Time of Onset	No. of Patients
With present attack of delirium tremens	18
Less than 8 months before present episode	4
Less than 3 years before present episode	2
Less than 5 years before present episode	3
Less than 7 years before present episode	1
Idiopathic epilepsy (began at age of 11)	1
Total	29

the present attack of delirium tremens. Of the remaining 11 patients, the duration of fits was less than eight months in 4, less than three years in 2, less than five years in 3 and less than seven years in 1 (table 1). The average age at onset of convulsions was 39 years. In only 1 patient, as mentioned before, did the onset of fits precede the alcoholism. He is the only patient of the group of 29 who may be considered as suffering from "idiopathic" or "essential" epilepsy, his fits beginning at the age of 11.

In 17 of the 29 patients the present attack of delirium tremens was ushered in by a fit; in the other 12 the convulsive episodes occurred only during the course of the delirium. The number of fits associated with the onset or course of the delirium varied from one to six, while 2 patients had status epilepticus. All but 1 patient had grand mal attacks. The exception was a white man aged 38 with a history of alcoholism for eighteen years. He had sustained a fracture of the skull at the age of 31. Two years later, at the age of 33, he began to have psychomotor equivalents associated with ingestion of alcohol. The physical, neurologic and laboratory examinations gave essentially normal results. An air encephalogram showed diffuse cortical atrophy and ventricular dilatation. No patient had or gave a history of petit mal attacks.

Injury to the Head.—Ten of the 29 patients had a reliable history of injury to the head. Three of these had sustained lacerations of the scalp during the alcoholic episode immediately preceding the onset of the delirium and convulsion. In the others the injury to the head preceded the onset of fits by a longer period and was associated with unconsciousness or fracture of the skull. In 7 of the 10 cases the onset of fits occurred from a few hours to two and one-half years after the injury to the head; in the other 3 cases the interval was much longer. In all but 1 case the alcoholism preceded the injury to the head by many years.

Physical and Neurologic Status.—The severity and duration of the delirium tremens in the patients with convulsions was similar to that in the patients without convulsions, and the physical findings were essentially the same in the two groups. Thus, in a number of the cases the liver was enlarged; in a few there was moderately intense vomiting, the material being blood tinged in some instances. The rectal temperature was over 100 F. in 25 of the 29 cases, the highest being 104.2 F. In 15 cases the leukocyte counts were 9,000 or over on admission, the highest being 28,000. Urinalysis showed slight albuminuria in 13 of the 29 cases; other urinary findings were normal except for a trace of sugar in some cases and hematuria and casts in 1 case. The blood pressure was considered elevated in 7 of the 29 cases, since the diastolic pressure was at least 105 mm. with a corresponding elevation of systolic pressure.

In no case were focal neurologic signs present. In 4 cases there was evidence of peripheral neuritis, while in 10 pupillary abnormalities ranging from a sluggish reaction to light or irregularity of outline to definite Argyll Robertson types were noted.

Serologic Reactions of the Blood and Spinal Fluid Findings.—The Kahn reaction of the blood was positive in 4 cases, associated in all instances with a negative Wassermann reaction of the spinal fluid.

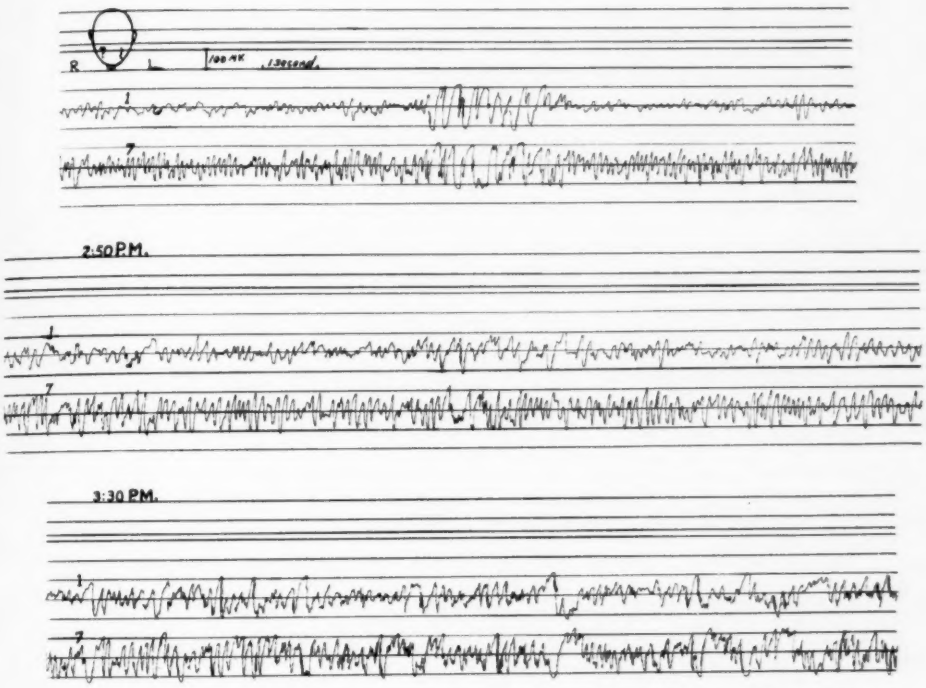
Data on the results of lumbar puncture are available in 28 of the 29 cases. In all the cases the Wassermann reaction of the spinal fluid was negative. The pressure was 180 mm. or over in 8 of the 28 cases (29 per cent). Cell counts were normal except in 1 case, in which there were 10 lymphocytes per cubic millimeter. The total protein content was normal (under 45 mg. per hundred cubic centimeters) in all but 1 case, in which it was 48 mg.

Treatment and Outcome.—All the patients received the routine treatment for delirium tremens used in this hospital,[2] and all recovered.

Encephalographic Studies.—Air encephalograms were made in 7 cases. All showed marked cortical atrophy with ventricular dilatation.

2. Rosenbaum, M.; Piker, P., and Lederer, H. D.: Delirium Tremens: A Study of Various Methods of Treatment, Am. J. M. Sc. **200**:677 (Nov.) 1940.

In 1 of these 7 cases electroencephalographic studies were done before and during the ingestion of whisky (90 proof).[3] Blood was drawn for determinations of the alcohol content at the same time that the electroencephalographic tracings were made. The patient was a 39 year old white man with a negative family history for convulsions. He had been drinking beer and whisky for fifteen years and had had delirium tremens on four occasions. At the age of 34 he had an injury to



A (upper two tracings), right and left frontal electroencephalograms taken with monopolar electrodes before the ingestion of whisky. Note the somewhat irregular alpha rhythm before and after the "paroxysm of pathologic waves."

B (middle two tracings), taken with the same leads as were the tracings in *A* fifty minutes after ingestion of a total of 8 ounces (240 cc.) of whisky (90 proof), given in three divided doses. The alcohol content of the blood is 165 mg. per hundred cubic centimeters. The voltage is increased, and there is a greater proportion of pathologic waves.

C (lower two tracings), taken one and a half hours after a total ingestion of 12 ounces (355 cc.) of whisky. The alcohol content of the blood is 251 mg. per hundred cubic centimeters. The voltage is still higher, and the tracing throughout resembles to some extent the "paroxysm of pathologic waves" noted in the first tracings (*A*).

3. The electroencephalograms were recorded at Longview State Hospital, Cincinnati.

the right side of the head. Two weeks later his first grand mal attack developed. Since then he has had grand mal seizures once a month, chiefly associated with alcoholism, but present occasionally between alcoholic episodes. Results of physical, neurologic and laboratory studies (including that of the cerebrospinal fluid) were normal. Air encephalograms revealed diffuse cortical atrophy with dilated ventricles. Electroencephalographic tracings were made after the patient had completely recovered from his last attack of delirium tremens. The electroencephalogram showed the alpha rhythm to be present but frequently distorted by slower than normal waves. At irregular intervals there were groups of high voltage waves which for the most part were slow (3 per second), but at times were rapid and had sharp peaks (grand mal type). The voltage of the tracing was definitely higher throughout on the right side (figure, *A*). After the ingestion of whisky the electroencephalogram showed progressive increase in voltage, which first became manifest on the right side, and increase in the proportion of pathologic waves over the whole cerebral cortex (figure, *B* and *C*). No convulsion occurred.

COMMENT

We have found that in 384 admissions for delirium tremens there were 32 instances of convulsions (8 per cent), i. e., 9 per cent of the 305 patients who constituted this series had convulsions. These percentages exceed the expectancy of convulsions in the general population (0.5 per cent).[4] It is of interest to speculate regarding the possible reasons for these findings.

The first possible explanation is that we are dealing with a group of patients with "idiopathic" or "essential" epilepsy. That this is not the case is indicated by the fact that the average age at onset of fits in this group was 39 years. Only 1 patient in the entire series may be considered as having idiopathic or essential epilepsy. Furthermore all the patients except this one had had many years of alcoholism preceding the first fit.

A second possibility is that this is a group of patients in whom factors of organic disease (apart from head injury) were responsible for their convulsive seizures. Practically all were febrile; half had leukocytosis; a large number had albuminuria; a few had an enlarged liver, gastritis, hypertension, peripheral neuritis or pupillary changes. These abnormalities may have been associated with the onset of convulsive seizures, but they were also present in the patients with delirium tremens who did not have convulsions and therefore could not in themselves have

4. Lennox, W. G.; Gibbs, E. L., and Gibbs, F. A.: The Inheritance of Epilepsy as Revealed by the Electroencephalograph, J. A. M. A. **113**:1002 (Sept. 9) 1939.

been the determining factors. It is significant in this connection that conditions which might in themselves be held responsible for fits, such as syphilis of the central nervous system or focal neurologic disease, were uniformly absent.

A third possible explanation of the high incidence of convulsions in patients with delirium tremens is the factor of injury to the head. A positive history of head injury was elicited in 10 of the 29 cases (34 per cent). In 7 of these 10 there seemed to be a close relationship between the occurrence of the head injury and the onset of fits. The incidence of head injuries in 171 patients with delirium tremens who did not suffer from convulsions was 8 per cent (table 2). We realize that in both groups the incidence of head injuries may have been greater than our figures indicate owing to the frequency with which such injuries received during alcoholic episodes are not recalled. Nevertheless, our figures seem to point to the importance of head injury as a contributing factor in producing fits in patients who have delirium tremens. We have noticed

TABLE 2.—*Comparative Incidence of Injuries to Head*

	Delirium Tremens With Convulsions (29 Patients)	Delirium Tremens Without Convulsions (171 Patients)
History of head injury	34% (10 patients)	8% (13 patients)
No history of head injury	38% (11 patients)	60% (103 patients)
No data	28% (8 patients)	32% (55 patients)

a tendency to the development of convulsions in patients with chronic alcoholism who have suffered a severe head injury if they continue to drink.

The fourth possible explanation is that the patients with convulsions were constitutionally predisposed to fits by virtue of an inherited cerebral dysrhythmia.[4] We have no electroencephalographic tracings for our patients before they had a fit. However, we have electroencephalograms for 4 patients who were suffering from chronic alcoholism complicated by convulsions, and these had pathologic brain waves of the types seen in convulsive disorders.

The work of Lennox, Gibbs and Gibbs [4] has made it clear that about 10 per cent of persons in the general population with no clinical history or evidence of epilepsy have a gross cortical dysrhythmia which may represent a predisposition to convulsive disorders. They have also noted that this latent predisposition may become clinically evident after an injury to the brain. The fact that 9 per cent of a large group of patients with delirium tremens had convulsions associated with their illness coincides with the aforementioned 10 per cent incidence of cortical dysrhythmia in the general population.

Assuming, then, that this predisposition to convulsions was present in our cases and knowing that alcohol does accelerate brain waves,[5] one may ask why so many years elapsed between beginning of the alcoholism and the development of convulsions. To answer this question several factors need to be evaluated.

The first factor is that alcohol itself accelerates brain waves. It might, therefore, be thought that this factor would be sufficient to induce convulsions in a susceptible person. However, our data indicate that this is not always the case. In support of this statement are the following facts: First, our patients drank for many years before the onset of convulsions. Second, the patient who was given alcohol during the course of electroencephalographic studies did not have a convulsion at the time, although his existing cerebral dysrhythmia became intensified. Third, in 40 per cent of our patients the convulsions did not occur until the delirium was in progress, by which time the patient had not taken alcohol for several days. Finally, 5 of the patients with repeated admissions had a convulsion on only one occasion.

The second factor is that of organic damage to the brain. In this series a large number (34 per cent) had head injuries. Moreover, all were addicted to alcohol for many years, a condition which in itself may lead to cerebral damage. In support of this statement is the fact that all the patients who had air encephalograms showed marked cortical atrophy with ventricular dilatation.

The final possible factor contributing to the onset of fits at this late date is the acute cerebral condition ("wet brain") and other metabolic disturbances of delirium tremens.

In summary, then, the following succession of events seems to explain best the late development of fits in these patients. In a person predisposed to convulsive disorders, the development of cerebral lesions, such as injury to the brain and alcoholic encephalopathy, probably lowers the convulsive threshold. In such a setting, the accelerating effect of alcohol on the brain waves plus the severe stresses of delirium tremens may induce a convulsion.

Other points in the analysis of the cases deserve comment. The presence of pupillary abnormalities in the absence of neurosyphilis indicates once more the damaging action of alcohol on the midbrain. In only 8 (29 per cent) of the 28 patients was the cerebrospinal fluid pressure increased, an observation which coincides with a previous finding [6] that 25 per cent of patients with acute alcoholism have increased cerebrospinal fluid pressure.

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5. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Cerebral Dysrhythmias of Epilepsy: Measures for Their Control, Arch. Neurol. & Psychiat. **39**:298 (Feb.) 1938.

6. Rosenbaum, M.; Herren, R. Y., and Merritt, H. H.: The Cerebrospinal Fluid in Acute Alcoholism, New England J. Med. **215**:914 (Nov. 12) 1936.

SUMMARY AND CONCLUSIONS

Of 305 patients with delirium tremens, 29, or 9 per cent, had convulsions as a part of their illness. Except for the convulsion, the delirium tremens of these 29 patients was similar to that of the patients who did not have convulsions. All 29 patients recovered, suggesting that convulsions associated with seizures of delirium tremens does not indicate a poor prognosis. All but 1 had a history of many years of alcoholism before the onset of fits, and the average age at onset was 39 years.

Thirty-four per cent of the patients who had convulsions gave a history of injury to the head, as compared with 8 per cent of the patients who did not suffer from convulsions. Air encephalograms were made in 7 cases, and all gave evidence of marked cortical atrophy and ventricular dilatation. None of the 29 patients had syphilis of the central nervous system or focal neurologic disease.

In successive electroencephalographic tracings made on 1 patient after the ingestion of whisky abnormal waves became progressively exaggerated and spread to all parts of the cerebral cortex. No convulsions resulted, however.

The finding that 9 per cent of a large series of patients with delirium tremens have convulsions associated with the disease coincides with the statement by Lennox and his associates that 10 per cent of the population has a cerebral dysrhythmia which may represent a predisposition to convulsions.

The factors that may cause convulsions to appear in patients with delirium tremens are (*a*) a constitutional predisposition to fits plus (*b*) cerebral lesions, such as injury to the head and alcoholic damage to the brain, which may lower the convulsive threshold plus (*c*) acute cerebral lesions and severe metabolic strains resulting from delirium tremens plus (*d*) the exaggerating effect of alcohol on existing abnormalities in the brain waves.

CYSTICERCOSIS OF THE BRAIN

REPORT OF A CASE WITH OPERATION

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Infestation of the human brain with Cysticercus cellulosae, larva of Taenia solium (porcine tapeworm), is a medical curiosity in this country, for the condition occurs principally in sections of the world in which poor sanitation exists. Man may harbor not only the adult intestinal worm but also the larvae, which reach the digestive tract in polluted water or food and then spread by way of the blood stream to various tissues of the body. The larvae have a predilection for the muscles and the central nervous system but may invade almost any part of the body.

In the nervous system the larvae are found in the meninges, the ventricles, the parenchyma of the brain and occasionally the parenchyma of the cord.[1] Usually they are numerous and scattered, giving a diversity of changing symptoms. Less frequently they are single or few and produce more discrete symptoms or none at all.[2] Convulsions are the most common of all the symptoms, and this has served to focus renewed attention on the disease in recent years.[3] However, aside from emphasizing the epidemiologic problem [4] and establishing the fact that cysticercosis of the brain must be given consideration in the etiology of epilepsy, distressingly little of constructive value has developed from studies of the disease.

From the Department of Surgery of the New York Hospital and the Cornell University Medical College.

1. Hare, C. C.: Cysticercus Cellulosae of the Brain: Report of Two Autopsies, J. A. M. A. **111**:510-515 (Aug. 6) 1938.

2. Sato, T.: Cystercerci in the Human Brain, Deutsche Ztschr. f. Nervenh. **27**:24-44, 1904.

3. (*a*) MacArthur, W. P.: Cysticercosis as Seen in the British Army, with Special Reference to the Production of Epilepsy, Tr. Roy. Soc. Trop. Med. & Hyg. **27**:343-363 (Jan.) 1934. (*b*) Dixon, H. B. F., and Smithers, D. W.: Epilepsy in Cysticercosis (Taenia Solium): A Study of Seventy-One Cases, Quart. J. Med. **3**: 603-616 (Oct.) 1934. (*c*) Alexander, A. J. P.: Epilepsy and Cysticercosis, Brit. M. J. **1**:966-967 (May 8) 1937. (*d*) Greig, E. D. W.: Clinical Recollections and Reflections: Cysticercosis and Epilepsy, Edinburgh M. J. **44**:522-529 (Aug.) 1937.

4. Maplestone, P. A., and Bhaduri, N. V.: Taenia Solium and Cysticercus Cellulosae in India, Indian J. M. Research **25**:155-161 (July) 1937.

No medical treatment is known for extinction of the larvae once infestation of the tissues has occurred. In the case of infestation of the brain little hope is held for recovery or improvement of symptoms except that in due course of time the convulsions may subside spontaneously, and this happens infrequently. Comparatively few persons with cysticercosis of the brain have been subjected to operation deliberately or by mistake in exploration for neoplasm. In the majority of the cases reported no improvement has followed operation, principally because it was impossible to remove all the cysticerci, or even all of the offending ones.

An attitude has evolved, therefore, that surgical intervention has no place in the treatment of cysticercosis of the brain.[5] Yet, in view of the occasional instance of but one or a few intracranial cysticerci, there should be some victims of the disease that might benefit by surgical treatment. Because of the limited number of accounts supporting the faint hope of the exceptional case, I wish to report my experience in which surgical removal of a cysticercus from the brain of a woman who had had symptoms for a year has resulted in apparent cure for four years.

REPORT OF CASE

Periodic convulsive seizures on the left side without loss of consciousness began in August 1935. A diagnosis of probable cysticercosis of the brain was made in March 1936. A general convulsion followed by left hemiplegia developed in July 1936. A single cysticercus was removed from the right motor cortex in July 1936. Complete recovery ensued, without return of symptoms during four years of follow-up observation.

V. R., aged 40, an unmarried American trained nurse, was admitted to the hospital July 16, 1936 with the following history.

Clinical History.—For the previous eight years she had been stationed at a Salvation Army Hospital at Moradabad, India, near Lahore, She was born in Sweden but lived in the United States for a number of years before going to India. She had formerly had good health but, while in India, had typhoid fever in 1924 and malaria in 1929. The malaria was prone to recur from time to time, and she was said to have been especially ill with it in 1931 and again in 1934.

In August 1935 (eleven months before admission to the hospital) she began to have frequent attacks of uncontrolled jerking, preceded by paresthesias, in the left upper extremity. An attack characteristically lasted about sixty seconds and was unaccompanied by loss of consciousness or other phenomena. For the next six months she had recurrent series of these convulsive seizures and was advised to leave India. In March 1936 she entered the London Hospital, England, under the care of Dr. George Riddoch. There she was found to have "only slight left pyramidal signs associated with jacksonian attacks." A lumbar puncture demonstrated normal cerebrospinal fluid pressure and a colloidal gold curve of

5. (*a*) Dandy, W. E.: Cysticercus Cellulosae, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12, pp. 399-404. (*b*) Dixon and Smithers.[3b] (*c*) Alexander.[3c]

0112321100 (cell count and protein content not reported). Calcified cysticerci were demonstrated roentgenographically in the muscles of the thigh, and a diagnosis of cysticercosis of the brain, probably multiple, was made. Bromides and arsenic were prescribed, and she was advised not to return to India.

She came to the United States in July 1936, having continued to experience occasional convulsive seizures. Until July 13 all attacks had been alike, but on this day the convulsive movements in the left upper extremity became prolonged, violent and associated with a painful burning sensation. She lay down, shortly lost consciousness and had, for the first time, a major convulsion involving all extremities and lasting for twenty minutes. But for slight headache and a feeling of lethargy for a few hours after the attack, she observed no untoward sequelae till the following day. Then she found the left upper and lower extremities to be weak and slightly numb. During the next three days the weakness was replaced by complete left hemiplegia, and in addition there were increasing generalized headache and drowsiness.

Examination.—She was well nourished and of good physical development. The pulse, temperature and respiration were normal, and the blood pressure was 118 systolic and 68 diastolic. No superficial nodules were discovered. The results of cardiac, pulmonary and abdominal examination were not remarkable, the abnormal findings being limited entirely to the functions of the nervous system.

She lay quietly in bed, complaining of dull generalized headache. She was somewhat drowsy and slightly sluggish in all mental reactions, but was cooperative and showed no impairment in memory and judgment.

There was moderate weakness of the facial muscles on the left. The optic fundi were abnormal in that the retinal vessels were unusually full and the optic cups were obliterated; the appearance was suggestive of low grade papilledema. Other cranial functions were not remarkable.

The left upper and lower extremities lay immobile, and only after concentrated effort could slight motion be initiated at the shoulder and hip. There was moderate flaccidity of these extremities on passive motion. Sensation was normal but for impairment in position sense, two point discrimination and figure writing on the left side. Deep reflexes were absent on the left, and there was an extensor plantar response on this side.

The urine was normal. The blood count was: hemoglobin content 15 Gm. per hundred cubic centimeters; erythrocytes 4,700,00 and leukocytes 7,000 per cubic millimeter, with a differential white cell count of 65 polymorphonuclear leukocytes, 23 lymphocytes, 2 monocytes and 11 eosinophils. Examination and culture of the stools showed no abnormality.

Roentgenograms of the skull, the chest and the upper extremities were normal, but those of the thighs showed several irregular, elongated calcific shadows, about 2 by 8 mm., assumed to be calcified cysticerci in the muscles.

Ventriculographic Study.—A ventricular needle was introduced into the occipital horn of the left lateral ventricle. The ventricular fluid was under moderately increased pressure. With an interchange of air, 25 cc. of fluid was withdrawn and an equal amount of air injected. The fluid was clear, and analysis showed no cells of any kind, 0.04 Gm. of total protein and 0.06 Gm. of sugar per hundred cubic centimeters and a colloidal gold curve of 1111000000. The roentgenograms showed adequate filling of the ventricular system, moderate depression of the anterior horn of the right lateral ventricle and a slight shift of the frontal horns to the left side.

Operation.—On July 22, 1936, after the patient had been anesthetized, a medium-sized right parietal bone flap was reflected and the central lobe of the cerebrum was exposed (fig. 1). In the motor area at the superior margin of the exposure was a small mass, about 2 cm. in diameter. It had a slightly rounded surface and appeared to be situated in or just beneath the cortex. The pia-arachnoid of the immediate region had a dull gray luster. Around the periphery of the mass in the subarachnoid space were grayish yellow collections and numerous small, probably new, blood vessels, indicative of an inflammatory process. On palpation the mass was discrete and firm. Elsewhere the meninges and cortex

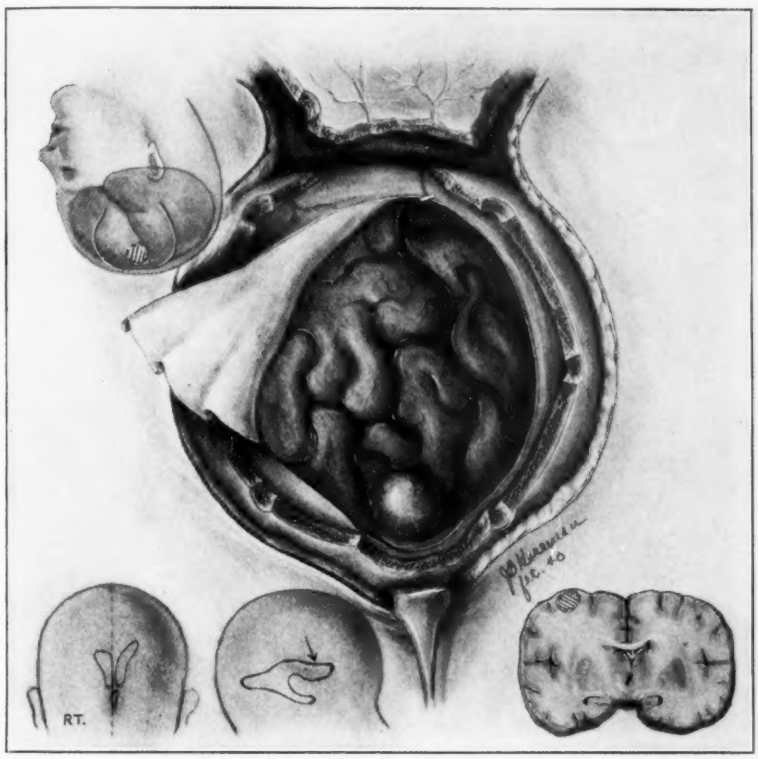

Fig. 1.—Appearance of the cysticercus cyst at operation. Insets show location of the lesion and the deformity of the ventricles demonstrated by ventriculograms.

were normal but for slight flattening of the gyri and narrowing of the sulci. A block of the cortex containing the thick-walled cyst of a cysticercus was excised with the endothermy needle. The wound was closed without decompression.

Pathologic Study.—Gross examination of the operative specimen disclosed a globular mass of reddish tissue, about 3 cm. in diameter, which was firm but flexible and somewhat elastic. Section revealed a central core, about 5 mm. in diameter, of what at first appeared to be inspissated pus; it was too soft and amorphous for one to be certain that it contained a parasite. Surrounding the

core was a yellowish, chitinous membrane, and outside this was a compact wall of apparently inflamed brain tissue, which was as much as 4 mm. in thickness except where the cyst wall approached to within a millimeter of the surface of the cortex.

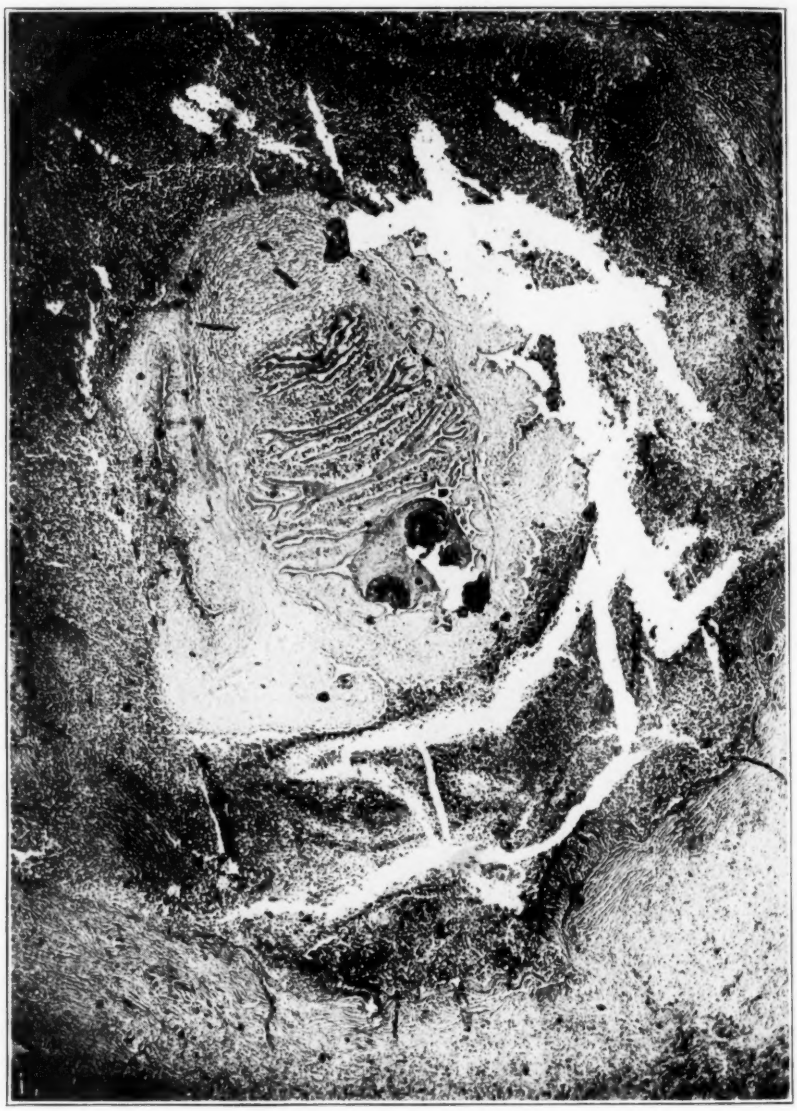

Fig. 2.—Low power photomicrograph showing the degenerating, encysted cysticercus and inflammatory reaction in the adjacent cerebral tissue.

Microscopic examination showed in the center of the section a cysticercus in fairly good state of preservation (fig. 2). It exhibited a well formed head with rostellum and hooklets, beneath which was the muscular organ of the rostellum,

with suckers at the sides. The head merged into the body, which was an arborescent, canal-like structure containing granular material and something resembling red corpuscles. Surrounding the larva was a mass of purulent material and outside of this a zone of connective tissue filled with chronic inflammatory cells and many giant cells. The brain tissue surrounding the connective tissue capsule showed marked vascularization, a heavy deposition of what appeared to be fibrin and many protoplasmic astrocytes and other reactive cells.

Postoperative Course.—The immediate postoperative recovery was prompt, and the wound healed without complication. During the first week facial motion returned to normal. In the second week motion began to improve rapidly in the left upper extremity but more slowly in the lower extremity. The patient was troubled by recurring unpleasant paresthesias in the left hand, but these gradually disappeared. After two weeks she got out of bed, and as strength in the lower extremity returned she came to walk with lessening limp. At the time of discharge, a month after operation, weakness of the left extremities was barely discernible, sensation was normal, she was free of headache, paresthesias and other untoward symptoms and there had been no further convulsive phenomena.

Additional Data.—The eosinophilia of the blood disappeared after operation, and the differential leukocyte count on discharge was normal. Lumbar puncture, performed thirty days after operation, showed the fluid to be clear and under normal pressure; the total protein was 0.030 Gm. per hundred cubic centimeters and the cell count zero.

Follow-Up Observations.—The patient has been examined annually during the four years since operation. She has never had a recurrence of convulsive seizures in any form. She has been free of headaches, paresthesias, hallucinations and other related symptoms. Since January 1937 she has been actively engaged in administrative nursing and considers herself in perfect health.

COMMENT

Since the patient had no knowledge of any illness which might mark the time of acquiring the disease, it is impossible to determine the interval before the onset of convulsions. It is a common observation that convulsions may be the first noteworthy manifestation of the disease, although a history of previous unexplained fever and general malaise may give a clue to the inception. Convulsions or other nervous symptoms have been known to occur within a few weeks after infestation with Taenia solium, while in other cases it is assumed that a number of years have intervened before the onset of symptoms attributable to involvement of the nervous system. The average interval is probably two to five years.

In this patient calcified cysticerci in the muscles of the thigh were demonstrated on a roentgenogram seven months after the onset of convulsions, and it has largely been true in the cases reported in detail by MacArthur [3a] and by Dixon and Smithers [3b] that calcified cysticerci were present in muscles by the time the patients were examined for convulsions. The time and degree of calcification of the larva and its

surrounding tissues depend on facts not understood,[6] but since calcification begins with the death of the larva, the time of its onset depends on the longevity of the larva. Thus, roentgenologic confirmation is unlikely within four or five years of infestation and may be further delayed.[7] Cysticerci in the brain on the whole probably die later than those in muscles and are less prone to calcify. Of 71 cases reported by Dixon and Smithers,[3b] calcification of cysticerci was observed in roentgenograms of the skull in but 3. Other single observations of intracranial calcification have been reported.[8]

It was of advantage to have the probable diagnosis made prior to the development of hemiplegia; otherwise the calcified bodies in the muscles of the thigh and the significance of eosinophilia of the blood might easily have been overlooked. The occurrence of strictly focal convulsions, followed after a period by the development of hemiplegia, favored the diagnosis of intracranial neoplasm. These symptoms were somewhat unusual for cysticercosis of the brain, since the usual symptoms are those due to multiple cysts in scattered locations and hemiplegia alone has been reported infrequently.[9] But the fact that intracranial cysticerci may exist in any number from one to several thousand, and in any location, emphasizes the unreliableness of any one clinical picture alone in making the diagnosis.

Intracranial cysticerci are found to exist, in the order of their frequency: (*a*) in the subarachnoid spaces, particularly in the basilar cisterns, where they tend to form racemose clusters,[5a] and in the cerebral sulci; (*b*) in the ventricles of the brain, and (*c*) in the parenchyma of the brain. According to Keuhelmeister,[10] of 88 cases, cysticerci were found over the surface of the brain in 55 per cent, in the ventricles in 24 per cent and in the substance of the brain in 21 per cent. Their principal occurrence in the fluid spaces in and about the brain suggests that they may be conveyed largely through the choroid plexuses; indeed, Hennenberg [11] mentioned finding the larvae in the choroid plexuses. Those found in the substance of the brain are more likely to have been carried directly to their location by the blood stream. In this case it

6. Morrison, W. K.: Cysticercosis in Twin Brothers, Aged Thirteen Years, with Radiological Study of Calcified Cysticercus in Twelve Cases, Brit. M. J. **1**:13-14 (Jan. 6) 1934.

7. Dixon and Smithers.[3b] Greig.[3d]

8. (*a*) Baker, A. B.: Cysticercosis of Central Nervous System, Minnesota Med. **19**:495-504 (Aug.) 1936. (*b*) Sorge, F.: Calcified Cysticercosis: Two Cases, Arch. f. klin. Chir. **185**:31-37, 1936. (*c*) Gallais, P.: Two Cases of Cerebral Cysticercosis with Epileptic Manifestations, Bull. Soc. path. exot. **31**: 915-919, 1938. (*d*) Morrison.[6]

9. Sato.[2] Alexander.[3c] Gallais.[8c]

10. Keuhelmeister, cited by Dobrotvorsky.[14c]

11. Hennenberg, cited by Hare.[1]

was difficult to determine whether the cysticercus was primarily parenchymal or whether it had become buried deep in a cerebral sulcus, although the latter is the more probable.

Of 128 collected cases of cysticercosis of the brain in which examination was made after death, Sato [2] found in 19 no symptoms of disease of the nervous system; in those in which lesions involved the cerebral cortex the expected symptoms, such as convulsions, hemiplegia and aphasia, were present, and in those in which cysts occurred in the ventricles (and there were 33 instances of solitary ventricular cyst—in the fourth ventricle in 22, in the lateral ventricles in 9 and in the third ventricle in 2) the symptoms were often the most formidable and the incidence of increased intracranial pressure was high. Detailed study of the changes that take place in the cysticerci and in the adjacent parenchyma, ependyma and meninges has contributed to the further understanding of the disease. MacArthur,[3a] giving particular attention to this aspect, was impressed with the likelihood that the larvae while alive are relatively well tolerated by the host but that after their death they act as irritants, as a result partly of their toxic effects and partly of the enlargement of the cysts by an increase in their fluid contents. That this was true of palpable cysts in the muscles and subcutaneous tissues was conclusively shown in his studies.

The pathologic findings in the cyst removed at operation in this case conform to those described by many other authors.[12] The larva was obviously dead, and although its form was still fairly well preserved, there was necrotic material inside the cyst wall, the wall itself was thickened and showed inflammatory reaction and there were active degeneration in the surrounding brain tissue and localized meningitis in the adjacent pia-arachnoid. There was no calcification as yet in the head of the larva or in the cyst wall, the two sites in which this change is found to occur after more advanced degeneration. Exactly what changes in the brain took place after the major convulsion to induce hemiplegia cannot be said. There were marked vascular changes in the degenerating brain surrounding this cyst which suggest that progressive alteration of tissue accounted directly for both the major convulsion and the subsequent hemiplegia. It is entirely possible that eventually there would have been spontaneous recovery from paralysis, but it can be said reasonably that removal of the irritating cysticercus greatly increased the chances of recovery.

The finding at operation of a local exudative process in the pia-arachnoid about the lesion suggests that changes consistent with menin-

12. (*a*) Bucy, P. C., and Huff, C. G.: Cysticercus Cellulosae of the Human Brain, Tr. Chicago Path. Soc. **14**:298-300, 1936. (*b*) Dolgopol, V. B., and Neustaedter, M.: Meningo-Encephalitis Caused by Cysticercus Cellulosae, Arch. Neurol. & Psychiat. **33**:132-147 (Jan.) 1935. (*c*) Hare.[1] (*d*) MacArthur.[3a]

gitis might have been found in the cerebrospinal fluid had a lumbar puncture been performed prior to operation; no abnormality was present in the ventricular fluid examined before operation or in the spinal fluid obtained a month later. Others [12b] have reported a variety of abnormalities of the cerebrospinal fluid, including increase in the total protein content, an abnormal colloidal gold curve and even fragments of cyst wall. Still others [3a] have stressed the point that there are no constant changes in the cerebrospinal fluid that can be relied on to determine the presence or absence of cysticercosis of the central nervous system.

In the presence of clinical evidence of increased intracranial pressure and contraindication to lumbar puncture, the possible aid that cerebrospinal fluid findings might lend to diagnosis may be denied the examiner. Other aids to diagnosis, such as dermal, complement fixation and precipitin tests, have been utilized, but the specific antigen for the tests is not readily accessible and the tests are said to be but 50 per cent positive in cases of cerebral cysticercosis.[8a] Thus, anything short of demonstration of the cysticerci at operation cannot be relied on implicitly to make the diagnosis of cysticercosis of the brain. In practice the diagnosis often becomes apparent when cysts in the soft tissues of the body are palpated or demonstrated by biopsy or in roentgenograms in a person with unexplained convulsions; clinical and laboratory tests may be of little or no additional assistance. But there is also the remote, though constant, possibility of the coexistence of infestation with cysticerci and another lesion of the nervous system.

The prognosis in cysticercosis of the brain with regard either to mortality or to morbidity is, on the whole, not good; so much depends on the number and location of the cysticerci. The mortality is unknown, for there are no reliable statistics on the incidence of the disease. But Dixon and Smithers [3b] reported 12 deaths from the direct effects of cysticercosis of the brain in their series of 71 cases; 6 patients died in status epilepticus, 2 with "meningeal symptoms," 2 with symptoms of cerebral tumor, 1 after operation for removal of cysts of the brain and 1 with "some form of encephalitis."

Adequate information is also lacking with respect to the spontaneous remission of convulsions and other nervous symptoms caused by the disease. Such information would have value in determining the advisability of operation in the occasional case in which it might be considered. From the data available it appears that even after sufficient time has elapsed in which it could be expected reasonably that cysticerci responsible for convulsions have degenerated completely, convulsions continue, probably owing to the remaining cortical scar. MacArthur [3a] mentioned that in 4 of his series of 60 cases fits ceased after a duration of from a few months to twenty years. In but 5 of the 71 cases of Dixon and Smithers [3b] were there spontaneous remissions: (1) fits for

twelve years, then none for two years; (2) fits for fourteen years, then none for four years; (3) fits for two years, then none for twenty-one years; (4) fits for three years, then none for twenty-four years, and (5) fits for thirteen years, then none for twenty-one years.

The operative removal of one cyst in this patient does not preclude the possibility of the presence of others, but if others do exist they did not in the past, nor do they now, give evidence of their presence. It may be assumed that the infestation occurred at least six or more years ago, and if other intracranial cysts exist, the likelihood of their producing symptoms decreases with the passage of time. While four years without symptoms may not be long enough for one to count on a cure of the disease, it is still sufficient to indicate the value of operative removal of the cysticercus. No cases have come to my attention in which convulsions have ceased spontaneously for any significant period and started again.

Doubtless the knowledge that cysticerci infrequently exist singly in the brain, plus the more or less unfavorable results in the comparatively few patients subjected to operation, has afforded ample reason for pessimism about the value of operation. Dixon and Smithers [3b] and Alexander [3c] stressed that diagnosis is important in cases of the disease because needless operation on the brain may thus be avoided. MacArthur [3a] concluded that "the large numbers of parasites found in the brain and their wide distribution there do not encourage a general resort to surgery." Dandy [5a] reported his experience in 2 cases and concluded that medical and surgical efforts are unavailing. Cairns [13] also reported 2 cases in which operation was unsuccessful and reasoned that there was no place for operative treatment in any but the rare case in which there might be "one or two cysts causing focal fits."

A somewhat more hopeful attitude toward the value of operation in cases of cysticercosis of the brain has been taken by others.[14] Dobrotvorsky,[14c] in 1930, reported 2 cases in which operation was performed and summarized the results in 24 additional cases gleaned from the literature. In 3 instances the operation involved the posterior fossa, and all the patients died. Of the remaining 23 patients having some type of craniotomy which exposed the cerebrum, 2 died shortly after operation, 2 died a few months after, 4 were unimproved, 2 were improved and 12 were "cured" (1 having been observed for five and

13. Cairns, H., in discussion on MacArthur.[3a]

14. (*a*) Horák, Janota and Jedlička, V.: Case of Cerebral Cysticercosis of Left Motor Region Causing Meningitis, with Recovery After Operation, Časop. lék. česk. **72**:1141-1144 (Sept. 22) 1933. (*b*) Akhundov, S. G., and Irger, I. M.: Late Results of the Surgical Intervention for Cysticercosis of the Brain, Khirurgiya, 1937, no. 12, pp. 57-60. (*c*) Dobrotvorsky, V. I.: Operative Treatment in Cysticercus of the Brain, Vestnik. khir. (nos. 58-60) **20**:97-103, 1930.

another for eleven years after operation). Horák, Janota and Jedlička [14a] reported success from operation in a single case which in many respects was like mine, although no follow-up period was mentioned. Akhundor and Irger [14b] reported temporary improvement in 3 cases after surgical intervention.

SUMMARY AND CONCLUSION

In cases of cysticercosis of the brain, when many larvae are present, there is no known medical treatment of value, and the results of surgical removal of one or several cysticerci have been largely disappointing This has led to an attitude of pessimism with regard to the value of surgical intervention in all cases, even though it has been recognized that occasionally but one or a few cysticerci may be present. The account of a case in which recovery for four years has followed the removal of a single cerebral cysticercus supports the value of operation in the occasional case in which there is evidence of limited infestation of the brain.

CHEMISTRY OF ANTICONVULSANT DRUGS

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Speculation as to the mechanism of convulsive attacks has been common since the dawn of scientific medicine. The assumption, so widespread in the last century, that epilepsy is a hereditary and constitutional disorder, without demonstrable structural abnormality, implies a chemical basis for the disease. This conception has received recent statistical confirmation.[1]

Modern methods of investigation have, to be sure, revealed structural abnormalities of the cerebral cortex in an increasing proportion of cases of epilepsy.[2] Even when such an abnormality exists, however, to say that it is *the* "cause" of the attacks is seriously to underestimate the importance of the underlying constitutional factor. Structural defects, such as scars or tumors, are unaccompanied by convulsions in the majority of instances. The incidence of blood relatives subject to convulsions in cases in which seizures appear after an injury is almost as high as in those cases in which no injury is apparent.[3] The electrical disturbances accompanying convulsions associated with a local gross lesion are usually widely distributed over the cortex.[4]

Many different aspects of the chemical metabolism of patients suffering from convulsions have been the object of intensive investigations

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1. Lennox, W. G.; Gibbs, E. L., and Gibbs, F. A.: The Inheritance of Epilepsy as Revealed by the Electroencephalograph, J. A. M. A. **113**:1002-1003 (Sept. 9) 1939.

2. Minkowski, M.: Pathologische Anatomie der Epilepsie, Schweiz. Arch. f. Neurol. u. Psychiat. **66**:697-699, 1936.

3. Lennox, W. G.: Epilepsies, in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1920, vol. 10, pp. 225-280.

4. Casamajor, L.; Smith, J. R.; Constable, K., and Walter, C. W. P.: Correlated Clinical and Electroencephalographic Findings in Children with Focal Convulsive Disorders, Arch. Neurol. & Psychiat., to be published.

since the beginning of the century. The research has until recently been unrewarding. It has been shown [5] that attacks may be precipitated in susceptible persons by overventilation. The tendency to seizures may be decreased in some cases by a ketogenic diet,[6] and petit mal attacks may be cut short by administration of carbon dioxide.[7] Paradoxically, however, the most important evidence for a fundamental chemical component in the disordered function of nerve cells leading to convulsions in human beings has been furnished by electrical records of the activity of the cortex (Lennox, Gibbs and Gibbs [8]) and by observations at the operating table (Penfield [9]).

From the electrophysiologic point of view, "epilepsy is a paroxysmal cerebral dysrhythmia"; [8] that is, typical convulsions are accompanied by characteristic alterations in the normal rhythm of potentials in the brain, usually over wide areas or in multiple foci. The abnormal alterations in potential are presumably primary to the convulsion, since they occur also between seizures observable clinically. They consist of an increase of voltage and alteration of rate in one or more portions of the cerebral cortex. Fast, high voltage waves are associated usually with grand mal convulsions, slow waves with psychomotor equivalents and alternations between fast and slow waves with petiti mal seizures. Each represents a fairly distinct physiologic entity, and it is probable that each should have separate consideration. Since, however, the various abnormalities may succeed each other in the same patient and since so little is known about the chemical implications of any of them, little attempt will be made to separate them here.

The most probable explanation for the small amplitude and rapid rate of the normal cortical rhythm and its decrease with cerebral activity is that it is the resultant of the irregular out-of-phase discharge of great numbers of cells. When a group of neighboring cells begins to discharge in phase and at an abnormally slow or fast rhythm, a convulsion is likely to occur. The localization of the disturbance is fairly constant at different times in each case. It appears that the cells from which it arises are to this extent abnormal.

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5. Rosett, J.: The Experimental Production of Rigidity, of Abnormal Involuntary Movements and of Abnormal States of Consciousness in Man, Brain **47**: 293-336, 1924. Foerster, O.: Hyperventilationsepilepsie, Deutsche Ztschr. f. Nervenh. **83**:347-356, 1925.

6. Wilder, R. M.: The Effects of Ketonemia on the Course of Epilepsy, Proc. Staff Meet., Mayo Clin. **2**:308, 1921.

7. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Influence of the Blood Sugar Level on the Wave and Spike Formation in Petit Mal Epilepsy, Arch. Neurol. & Psychiat. **41**:1111-1116 (June) 1939.

8. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Epilepsy: A Paroxysmal Cerebral Dysrhythmia, Brain **60**:377-388, 1937.

9. Penfield, W.: The Circulation of the Epileptic Brain, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:605-637, 1938.

When alterations of electrical potential occur in systems of electrolytes separated by semipermeable membranes, the existence of concomitant chemical changes can be predicated. The larger the one, the larger must be the other. There is, further, some direct evidence that the chemical disturbance accompanying cortical dysrhythmias are also abnormal and perhaps to some extent specific.

Gibbs, Lennox and Gibbs [10] have recently shown that in patients subject to petit mal the level of carbon dioxide in both carotid arterial and jugular venous blood tends to be abnormally low, while in those subject to grand mal it tends to be abnormally high. Their data indicate that the alteration in the level of carbon dioxide is primary to the convulsion, but also that it is not the sole chemical abnormality involved.

There are now available careful visual observations on the cerebral cortex during convulsions induced by local electrical stimulation. Penfield [9] has observed the spread of an area of vasodilatation over the cerebral cortex corresponding to the spread of the associated jacksonian attack. His observations strongly suggest that diffusion of a metabolite of small molecular size occurs—a description which closely fits carbon dioxide. Experimental convulsions produced by injection of camphor in dogs are preceded by a shift of p_H in the direction of alkalosis and produce a decrease in p_H locally.[11] The p_H of the cortex may differ from that of the blood.[9]

EXPERIMENTAL EVIDENCE OF A CHEMICAL COMPONENT OF CONVULSIONS

Convulsions may be produced in normal animals (or human beings) by administration of certain chemical compounds. Many, of course, are complex substances, such as camphor, thujone, strychnine and picrotoxin, which produce their effects by mechanisms unknown. One is in a better position to speculate about other alterations in the chemical milieu which are more nearly "physiologic," such as hypoglycemia, anoxia of certain types, acapnia and the effects of administration of ammonia or its salts. In a broad sense, all of these alterations affect tissue respiration, as has been demonstrated for most of them in tissue slices by means of the Warburg technic.[12]

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10. Gibbs, E. L.; Lennox, W. G., and Gibbs, F. A.: Variations in the Carbon Dioxide Content of the Blood in Epilepsy, Arch. Neurol. & Psychiat. **43**:223-239 (Feb.) 1940.

11. Dusser de Barenne, J. G.; Marshall, C. S.; McCulloch, W. S., and Nims, L. F.: Observations on the p_H of the Arterial Blood, the p_H and the Electrical Activity of the Cerebral Cortex, Am. J. Physiol. **124**:631-636, 1938.

12. Wortis, S. B.: Respiratory Metabolism of Excised Brain Tissue: II. The Effects of Some Drugs on Brain Oxidations, Arch. Neurol. & Psychiat. **33**:1022-1029 (May) 1935.

CHEMICAL SIMILARITIES AMONG ANTICONVULSANTS

In recent years, a more precise knowledge of the relative effectiveness of various chemicals as anticonvulsants has been acquired.[13] The substances so far known to be effective under one circumstance or another are as follows:

Carbon dioxide [10]
Dextrose [7]
The soluble bromides [14]
The soluble salts of magnesium [15]
Acetoacetic acid [16] (fig. 1)
Pyruvic acid [16] (fig. 1)
Practically all hypnotics in doses sufficient to produce anesthesia [13]
Certain synthetic compounds [17]

Synthetic Anticonvulsants.—The following categories are included.

Group I: Ketones and Oximes (fig. 1)

Phenyl ketones: acetophenone (and oxime); propiophenone;[14] phenylpropyl,[14] phenyl-n-butyl [14] and phenyl-n-amyl ketones;[14] benzoin oxime.

Benzyl ketones: Benzylmethyl ketone (and oxime); dibenzyl ketone; benzal acetone; methyl-p-tolyl ketone; acetylbenzoyl ketone; benzoyl acetone; furylphenyl ketone.[18]

Group II: Phenyl Barbiturates and Hydantoins (fig. 2)

Phenylethyl [14] and phenylethylmethyl [14] barbituric acids; diphenyl, phenylethyl and methylbisphenyl hydantoins (see also group VI).

Group III: Benzoxazoles (fig. 2)

Methyl, ethyl, propyl, hexyl and benzyl benzoxazoles.

Group IV: Sulfur Compounds (fig. 1)

Ethylphenyl sulfide and sulfone; ethylphenyl, propylphenyl, isopropylphenyl and diphenyl sulfoxides.

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13. Merritt, H. H., and Putnam, T. J.: A New Series of Anticonvulsant Drugs Tested by Experiments on Animals, Arch. Neurol. & Psychiat. **39**:1003-1015 (May) 1938.

14. Hypnotic drug.

15. Hirschfelder, A. D., and Haury, V. G.: Low Plasma Magnesium and High Plasma Potassium in Essential Epilepsy, J. Pharmacol. & Exper. Therap. **57**: 127, 1936.

16. Keith, H. M.: Factors Influencing Experimentally Produced Convulsions, Arch. Neurol. & Psychiat. **29**:148-154 (Jan.) 1933.

17. Merritt, H. H.: Unpublished data. Wortis.[12]

18. Toxic drug.

Group V: Miscellaneous Phenyl Compounds

Phenyl semicarbazide;[18] benzyl carbamate;[18] phenyl propionamide;[18] phenyl glycol;[14] diphenyl acetic acid.[18]

Group VI: Cyclic Structures Without Phenyl

Cyclopentenylallyl,[14] diallyl,[14] ethylisoamyl[14] and pentenylethyl[14] barbituric acids; ethylisoamyloxymethyl hydantoin.[14]

Group VII: Aldehydes

Paraldehyde.[14]

It must be constantly borne in mind that of the substances tested, some found inactive might be effective if administered in a slightly different manner. Thus, neutral diphenyl hydantoin administered dry in capsules is ineffective, and its absorption and anticonvulsant action are obtained only by forming the sodium salt or dissolving the neutral material in oil.

Characteristics of "Physiologic" Anticonvulsants.—To begin at the top of the list, the fact that inhalation of an atmosphere containing about 5 per cent of carbon dioxide causes inhibition of petit mal attacks and their characteristic dysrhythmias in human subjects has already been pointed out.[7] The abnormal slow waves are more strikingly controlled than the abnormal fast ones, an effect to be compared with that of the same gas on the respiratory center.[19] Exposure to abnormally high concentrations of carbon dioxide does not produce rapid, high voltage disturbance, however; indeed, in animals it raises the threshold at which convulsions of the grand mal type (ordinarily accompanied by abnormally fast waves) are produced by electrical stimulation. Hyperpnea, producing a reduction of the carbon dioxide content of the blood, may precipitate a petit mal convulsion in a susceptible person, or a grand mal attack may occur when the hyperventilation is terminated.[10] Active nerve cells are, of course, constantly producing carbon dioxide.

The effect of dextrose is singularly parallel with that of carbon dioxide. It inhibits particularly the slow waves characteristic of petit mal.[7] Hypoglycemia is especially likely to precipitate petit mal attacks, and at the same time it raises the p_H of the cortex.[20] In normal human beings[21]

19. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Cerebral Dysrhythmias of Epilepsy: Measures for Their Control, Arch. Neurol. & Psychiat. **39**:298-314 (Feb.) 1938.

20. Marshall, C.; McCulloch, W. S., and Nims, L. F.: p_H of the Cerebral Cortex and Arterial Blood Under Insulin, Am. J. Physiol. **125**:680-682, 1939.

21. Hoagland, H.; Rubin, M. A., and Cameron, D. E.: The Electroencephalogram of Schizophrenics During Insulin Hypoglycemia and Recovery, Am. J. Physiol. **120**:559-570, 1937.

and in animals [22] hypoglycemia produces unconsciousness accompanied by large slow waves suggestive of those which occur in petit mal attacks.[7] Consciousness and a normal rhythm are restored by administration of dextrose, certain other sugars or glycogen, but (in animals) not by the better known products of the metabolism of dextrose, such as

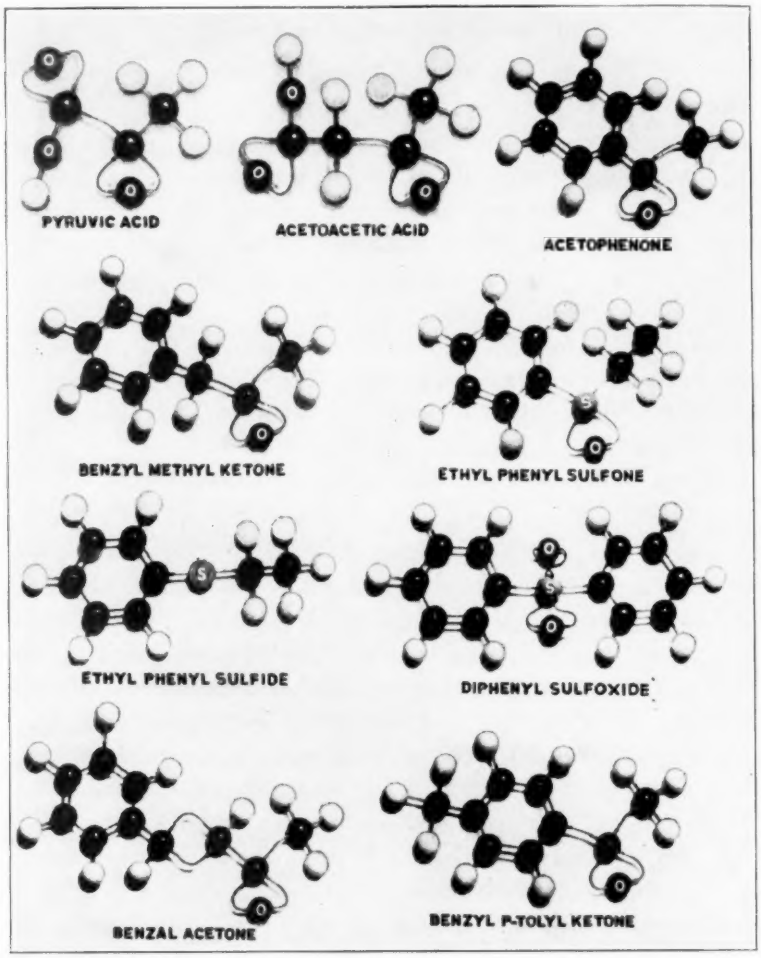

Fig. 1.—Structural formulas of pyruvic and acetoacetic acids, typical aromatic ketones and sulfur-containing anticonvulsants. In this figure and in the accompanying figure, black indicates carbon; white, hydrogen; *O*, oxygen, and *S* sulfur.

lactic, succinic, fumaric and pyruvic acids, hexose diphosphate, glyceric aldehyde and glutamic and adenylic acids—all of which can be utilized

22. Maddock, S.; Hawkins, J. E., and Holmes, E.: The Inadequacy of Substances of the "Glucose Cycle" for Maintenance of Normal Cortical Potentials During Hypoglycemia Produced by Hepatectomy with Abdominal Evisceration, Am. J. Physiol. **125**:551-565, 1939.

in the metabolism of muscle. Apparently, the cells of the brain require the intact dextrose molecule or a similar one for their normal function.[22] There is good evidence that glycolysis is the chief or only source of energy for nerve cells [23] and that dextrose and, especially, glycogen are broken down to lactic acid by brain tissue in vitro.[24] Brain tissue from pancreatectomized animals is as effective as that from normal animals.[24] Hyperglycemia may raise the lactic acid content of the brain as much as 200 per cent.

These various data suggest that it is not the intact dextrose or glycogen molecules themselves but rather metabolic products, such as

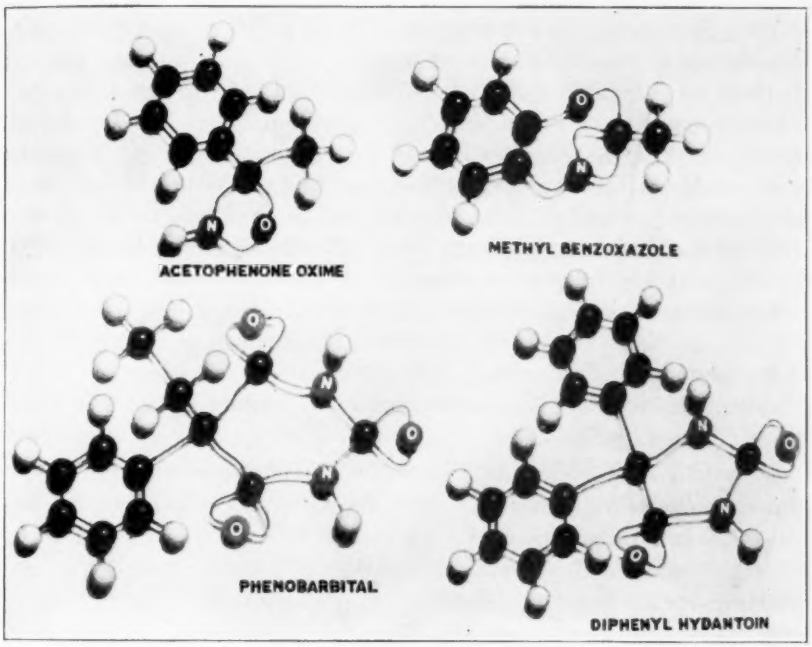

Fig. 2.—Structural formulas of an oxime, a benzoxazole, phenobarbital and diphenyl hydantoin. *N* indicates nitrogen.

lactic acid, formed within the cell which tend to inhibit convulsions and the slow waves associated with them.

Acetoacetic acid and other substances, such as betaoxybutyric acid, are products of incomplete breakdown of fatty acids. Among them are presumably the substances effective in inhibiting convulsions through the use of the ketogenic diet.[6] Acetoacetic and pyruvic acids have, in addi-

23. Holmes, E., and Sherif, W. H. F.: Relationship Between Sugar in Blood and Lactic Acid in Brain, Biochem. J. **26**:381-387, 1932.

24. Gerard, R. W.: The Metabolism of Brain and Nerve, in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1937, vol. 6, pp. 419-444.

tion, been shown to raise the threshold against experimental convulsions.[16] As acetoacetic acid is derived from fats, it is unlikely that it is normally produced in nerve cells, and to affect them it must reach them from without.

The bromides and the salts of magnesium occupy a unique position among anticonvulsant drugs, as they are not broken down in the body and are not known to be of importance in normal metabolism. In vitro, they retard oxygen consumption of slices of brain.[12] We have no grounds for speculation as to the mode of their action and cannot fit them into any scheme.

Most of the hypnotics of the alcohol and barbituric acid series can scarcely be regarded as anticonvulsants at all. Ether and ethyl alcohol, indeed, sometimes produce convulsions.[25] Abnormally slow cortical rhythms are produced during anesthesia by such hypnotics. Pharmacologists have pointed out certain physical and chemical similarities which run through most members of the barbiturate group. They are more soluble in lipoids than in water, and the coefficient of their partition between lipoids and water is high enough to permit them to penetrate cell membranes and to hinder their excretion by the kidneys. Their hypnotic effect is roughly proportional to the number of straight chain carbon atoms which they contain (Richardson's law). All of the more complex members are broken down in the organism, yielding, among other substances, ethyl alcohol or its intermediary breakdown products. Excellent summaries of the subject have been given by May and Dyson [26] (page 56) and by Fraenkel [27] (page 510).

Characteristics of the Synthetic Anticonvulsants.—A study of the physical and chemical characteristics of the compounds possessing marked anticonvulsant properties with little or no hypnotic effect permits the following provisional generalizations. For a general discussion of the principles involved and for references, May's little book [26] and Fraenkel's more complete treatise [27] may be consulted.

1. All such substances have low solubility in water (at neutrality) and high solubility in fat solvents (a high distribution coefficient). Any alteration in the molecule which produces solubility in water destroys the activity of the substances: for example, the change from acetophenone, $C_6H_5.CO.CH_3$, to benzoic acid, $C_6H_5.CO.OH$; or the change from propiophenone to its sulfonate, $NaO_3S.C_6H_4.CO.CH_2.CH_3$. Most members of the series are liquid at body temperature.

25. Payne, R. V.: Ether Convulsions, Guy's Hosp. Rep. **86**:461-475, 1936. Lundy, J. S., and Tuohy, E. B.: General Anesthesia Complicated by Convulsions, J. A. M. A. **108**:971-972 (March 20) 1937.

26. May, P., and Dyson, G. W.: Chemistry of Synthetic Drugs, ed. 4, London, Longmans, Green & Company, 1939.

27. Fraenkel, S.: Die Arzneimittel-Synthese, ed. 6, Berlin, Julius Springer, 1927.

Substances actually insoluble in plasma would, of course, fail to be carried to the nervous system. The significance of the high distribution coefficient of anticonvulsants is presumably the same as that of the high coefficient of most synthetic hypnotics. The latter is usually interpreted as permitting penetration of the substance into the membrane of nerve cells (May and Dyson,[26] page 43, and Fraenkel,[27] page 47).

2. Practically all substances in the series contain at least one phenyl nucleus in a terminal position (exceptions: the compounds in groups VI and VII. Feeble anticonvulsant properties are possessed also by pyruvic and acetoacetic acids and by methylethyl and diethyl ketones). If two phenyl nuclei occur, they are both attached to the same carbon (or sulfur) atom, or they are at opposite ends of a straight chain.

The phenyl nucleus is seldom broken down in the body. The fate of a number of ketones has been studied (reviewed by Thierfelder and Daiber [28]). These include acetophenone, propiophenone, butyrophenone, phenylbutylmethyl ketone, benzylmethyl ketone and benzylpropyl ketone. Thirty-five and seven-tenths per cent of acetophenone administered is reduced to the carbinol $C_6H_5.CHOH$, and 24.3 per cent is oxidized to benzoic acid, $C_6H_5.COOH$. About 40 per cent is completely destroyed. The other aromatic ketones behave in a somewhat similar way; they are in part reduced to the corresponding carbinol (without change in the length of the chain) and in part oxidized to benzoic acid, irrespective of the length of the chain. Certain ketones (phenylbutylmethyl ketone, benzylisopropyl ketone) give rise to phenyl urea.[29] Administration of diphenyl hydantoin to human beings causes a slight increase in the excretion of benzoates (Gray [30]).

3. Usually, if any other group is attached to this terminal phenyl nucleus the substance becomes inactive—for example, the following derivatives of acetophenone: p-bromacetophenone, methylbetanaphthyl ketone, p-aminoacetophenone and resacetophenone, and the following derivatives of benzophenone: phenyltolyl ketone and p-acetoxy, p-hydroxy and p-methoxy benzophenones. Exceptions are methyl-p-tolyl ketone and diaminodiphenylsulfone, which has feeble anticonvulsant properties.

The pharmacologic effect and process of breakdown of phenolic compounds are usually profoundly affected by substitutions in the ring (May and Dyson,[26] pages 24 and 40). In vitro, the presence of a second additive group on a phenol ring modifies the reactivity of the first, in general decreasing it. If several side chains occur on a ring, usually only one is oxidized (Fraenkel,[27] page 193).

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28. Thierfelder, H., and Daiber, K.: Zur Kenntnis des Verhaltens fettaromatischer Ketone im Tierkörper, Ztschr. f. physiol. Chem. **130**:380-396, 1923.

29. Hermanns, L.: Ueber den Abbau der Beta-Ketonsäuren im tierischen Organismus, Ztschr. f. physiol. Chem. **85**:233-240, 1913.

30. Gray, M. G.: Personal communication to the authors.

4. Adjacent to the terminal phenyl group, or separated from it by not more than two atoms (usually of aliphatic character), is a "reactive" group containing a double bond, usually 0-0, which is not terminal. Other "reactive" groups found in the series are CNOH, SO_2,SO and the benzoxazole linkage. Exceptions are phenyl glycol ($C_6H_5.CHOH.CH_2OH$), diphenyl acetic acid and the substances in group V.

Most of the anticonvulsants can, therefore, be regarded as mixed ketones or their equivalents. The oximes are readily hydrolyzed to form ketones. Little is known about the behavior of the sulfur compounds of the types in the list.

It has long been known that endogenous ketones have a soporific effect, and their anticonvulsant properties have been employed for therapeutic purposes, as has been pointed out.[31]

If we are justified in assuming that members of the group of compounds under discussion enter the membrane of nerve cells and are there broken down, it is attractive to suppose that they are broken down at the "reactive" radical, as occurs readily in vitro, e. g., by oxidation, either in such a manner that the carbonyl group becomes oxidized to a carboxyl group remaining attached to the smaller alkyl group (if there is a choice), or by oxidation of the terminal alkyl groups, leaving the next lower acid. As has been pointed out, acetophenone and other aromatic ketones are broken down in such a manner in the body to benzoic acid. That such an oxidation occurs chiefly in nerve cells is of course only a matter of inference.

5. There may be other "reactive" groups in the molecule, but if so they are separated by "nonreactive" C or N groups (exceptions: phenyl glycol and acetylbenzoyl ketone). This alternation between "reactive" and saturated radicals naturally suggests multiple points of scission.

6. Double bonds occur only in the "reactive" groups or in rings. Exceptions are the allyl compounds and benzal acetone, $C_6H_5.CH:CH.CO.CH_3$. The presence of double bonds, especially in the chain of a molecule, usually confers toxic properties on it (Fraenkel,[27] page 124). The grouping CH:CH.CO found in benzal acetone has many of the properties of a ketyl group and is readily oxidized to a carboxyl group.

7. The presence of $CH_2.CH_3$ groups or longer similar chains attached to the "reactive" group causes the appearance of sedative and toxic effects, as might be expected on general pharmacologic principles (Richardson's law).

8. In only one effective anticonvulsant of the group (benzyl carbamate) is there a linkage through an –0– atom, and this substance shows the toxicity which might be expected. The only effective furyl

31. Wilder.[6] Keith.[16]

compound, furylphenyl ketone, shows its expected toxicity. The three substances containing a terminal $-NH_2$ (phenyl carbazide, benzyl carbamate and phenyl propionamide) are all toxic.

9. In only one effective anticonvulsant of the group (diphenyl acetic acid) is a terminal –COOH group found.

The presence of a carboxyl group usually causes the substance to be more soluble in water than in lipoids and, therefore, inactive in moderate doses, or else to become conjugated with glycuronic acid, and so inactivated. Contrary to the usual rule, this carboxylic acid compound is definitely toxic, perhaps because of its high partition coefficient.

10. There is only one alcohol in the series, phenyl glycol, which is sedative. Its structure suggests that it also may readily be oxidized to benzoic acid.

11. The only ring structures containing "reactive" groups found in the effective compounds are the barbituric acid and the hydantoin derivatives. Both of these include two nitrogen atoms in the ring, adjacent to "reactive" groups. A possible significance of the alternation of NH_2 and CO groups in such rings is that scission easily takes place at these junctures. Such is, at least, the case with hydantoin in vitro.

COMMENT

From the description just given, it may be seen that certain physical and chemical peculiarities are typical of the synthetic anticonvulsants. While the range of structure among the effective compounds is fairly large, the compounds constituting exceptions to the generalizations presented are for the most part sedative or toxic. The anticonvulsants which have low toxicity and only the slightest sedative effects form a rather homogeneous group.

Theoretic Consideration: Normal and Artificial Anticonvulsant Substances.—The evidence which has been outlined strongly suggests that at least one aspect of the normal threshold against convulsions is a chemical one and that, conversely, an abnormal susceptibility to convulsions is the result of a chemical deficiency or abnormality, either in the plasma or in the brain itself. In the majority of cases, the abnormality—whatever its nature—can be demonstrated to be widespread over the cortex. If the abnormality is in nerve cells alone or predominantly, it would seem to consist of an inability to utilize nutritive materials offered to cells in a manner adequate to stabilize normal rhythms. An abnormality in the control of capillaries is a possible alternative explanation.[32] The stabilizing substance might then be regarded as a metabolite, perhaps of definitely acid nature. Whether the benzoic

32. Nims, L. F.; Gibbs, E. L.; Lennox, W. G.; Gibbs, F. A., and Williams, D.: Adjustment of Acid-Base Balance of Patients with Petit Mal Epilepsy to Overventilation, Arch. Neurol. & Psychiat. **43**:262-269 (Feb.) 1940.

acid presumably formed within cells by the breakdown of the synthetic anticonvulsants has some specific quality beyond its resistence to oxidation is a still more speculative question.

It is possibly of significance that a number of the effective substances considered here have been shown to be susceptible to two paths of modification in the organism. One is a reduction to a complex organic carbinol, presumably capable (in the brain) of retarding metabolism and showing cortical rhythms. The other is an oxidation to a stable aromatic acid, capable of stimulating cortical metabolism and rate of discharge and at the same time of liberating considerable energy.

Viewed from this aspect, the use of synthetic anticonvulsants would appear to be in the nature of a substitution therapy. Some of the substances aforementioned are normal constituents of the body; others (the synthetic phenyl derivatives) are closely allied chemically to normal endogenous products of metabolism. If so, their use would promise to be the most "physiologic," conservative and satisfactory method of treating convulsions—as indeed there is reason to think it is. A choice of them should be made on the basis, first, of safety to life; second, of effectiveness, and, third, of relative freedom from undesirable effects, such as drowsiness. On all of these counts, the only one of the new synthetic anticonvulsants so far introduced into clinical practice appears superior to phenobarbital, formerly the standard.[33] It is conceivable that some of the others will prove even more effective in certain cases.

SUMMARY

A review has been given of the reasons for supposing that the cortical rhythm is normally stabilized by endogenous metabolites and that the paroxysmal cortical dysrhythmias of epilepsy are dependent on a deficiency of such metabolites or an abnormal response to them.

There is reason to believe that both the "physiologic" anticonvulsants, such as dextrose, carbon dioxide, pyruvic acid and acetoacetic acid, and the synthetic anticonvulsants produce their effect by giving rise to an acid milieu within or about nerve cells.

The synthetic anticonvulsants, now a large and fairly distinctive group, are predominantly of a composition which suggests that they are broken down by cellular activity—perhaps chiefly within the brain—giving rise to stable acid products, such as benzoic acid. Their anticonvulsant activity has been shown to be entirely independent of any hypnotic activity.

It is suggested that the use of anticonvulsants in the treatment of epilepsy may be regarded as a substitution therapy.

33. Merritt, H. H., and Putnam, T. J.: Sodium Diphenyl Hydantoinate in the Treatment of Convulsive Disorders, J. A. M. A. **111**:1068-1073 (Sept. 17) 1938.

DIFFERENTIAL DIAGNOSIS OF HYSTERICAL TREMOR

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Hysterical tremor is a phenomenon which occurs rather often. It is a symptom which is sometimes difficult to differentiate from organic forms of tremor. The tremor may have the frequency and amplitude of rapid vibration, but sometimes there are only 5 or 7 movements to the second. Some forms of this tremor increase during active movement. In other forms the similarity of the tremor to the tremor in paralysis agitans is great. In some neuroses, especially of the traumatic type, the tremor has been found to become progressively greater in amplitude and finally to change into a myoclonus of great irregularity.

This description follows closely that of Oppenheim.[1] The descriptions in other textbooks are similar. I might add that it is characteristic of the tremor in hysteria that it is dependent on the situation to a high degree, is changing and is invariably connected with muscular tension, since it is possible only on the basis of a permanent effort. If one moves the shaking limb of the patient gently so that it relaxes the tremor disappears almost invariably. However, in some patients the tensions and the shaking continue. It is not always easy, even for the experienced, to make the differential diagnosis of hysterical or more general psychogenic tremor and the tremor in organic illness. It seems worth while, therefore, to draw the attention to a simple method of differential diagnosis of hysterical and organic tremor which has proved its usefulness. This method deserves some attention also from the point of view of the general physiology of posture in man.

When a subject is told to stretch his hands horizontally forward (with the eyes closed) and to keep this position the arms start to diverge. The outward deviation of the arms is symmetric. The subject does not know about the deviation as long as it does not surpass 8 to 10 cm. (to each side). If the deviation becomes greater some attempts at correction may be made. However, in many normal persons the deviation is much more outspoken. This deviation takes place only when both arms are

† Dr. Schilder died Dec. 8, 1940.

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1. Oppenheim, H.: Lehrbuch der Nervenkrankheiten, ed. 7, Berlin, S. Karger, 1923, p. 1713. This part has been worked over by Nonne.

outstretched. None takes place if only one arm is extended; that is, one outstretched arm can be maintained correctly in its position. If the subject, on the other hand, is told to stretch out the arms with an innervation stronger than that necessary to maintain the posture the arms converge toward the midline. This convergence takes place also when only one arm is stretched forward. The subject is unaware of this deviation, as of the divergence already described. This movement toward the midline takes place in the shoulder, the elbows remaining completely extended,[2] and is probably due to the fact that the power of the adductors in the shoulder girdle is greater than the power of the abductors, under these special conditions.

When patients with paralysis agitans are ordered to stretch their arms forward convergence occurs (especially outspoken in severe forms). This convergence is present as well when one as when both arms are stretched forward. Observation shows that this convergence occurs in the elbows. In other words, it is an expression of a prevailing flexor rigidity. If one fixates the elbows in extension and repeats the experiment the same divergence is present as is observed in the normal subject. In other words, the tendency to divergence in the shoulders is not impaired in patients with paralysis agitans. The convergence of the arms is due to prevalence of the flexor tone and is one of the most sensitive signs of flexor rigidity in the upper extremities. One finds it not in cases of paralysis agitans alone but in those of encephalitis and alcoholism.[3]

In all the patients with hysterical tremor I have had the opportunity of examining in the last few years I have found invariably that the outstretched arm or arms in which tremor was present showed convergence toward or deviation from the midline. This deviation occurred not from the elbow but from the shoulder girdle. A particularly instructive case may be reported.

REPORT OF A CASE

J. K., of Irish extraction, came to the mental hygiene clinic of Bellevue Hospital with the complaint that a persistent tremor of her right arm made it impossible for her to work. This tremor had started in September, when her 30 year old brother was married. She had to take care of her whole family, consisting of her mother, her sister and her sister's 4 children, all under 6 years of age. (The sister was separated from her husband.) Her father was alcoholic and had to be admitted repeatedly to the Psychiatric Division of Bellevue Hospital. The patient was annoyed by the children and slapped them often with the right arm. As a pencil packer she had used her right hand a great deal. She denied mas-

2. Hoff, H., and Schilder, P.: Die Lagereflexe des Menschen, Berlin, Julius Springer, 1927.

3. Schilder, P.: Clinical Note on Convergence Reaction, Especially in Alcoholics, J. Nerv. & Ment. Dis. **71**:732-734, 1930; Paralysis Agitans Pictures in Alcoholics, ibid. **76**:586-588, 1932.

turbation and emphasized that she had no interest in and no chance to be with men, since she went out only with her mother. She also slept in the same bed with her mother. She denied having hostile tendencies toward her father or her mother. Objective examination showed calcification of the choroid plexus. The internal organs were normal. The eyegrounds did not show any abnormality. There were no pathologic reflexes. Sensibility was normal, as were the special senses. The patient showed a persistent tremor in the right arm, which was localized chiefly at the wrist but was also present in minor degree at the elbow. The fingers were moved passively by the tremor of the hand. The tremor became particularly apparent when the arms were stretched forward. Only the right arm deviated inward at the shoulder, whereas the left arm when stretched forward with the right arm deviated slightly outward. The tremor had the frequency of approximately 20 per second and consisted of irregular shaking of the wrist up and down and sometimes also to the right and left. During the shaking over-innervation of the arm was noticeable. If one succeeded by cautious passive movements and by distraction of the patient's attention in relaxing the right arm the tremor disappeared. When the patient was told to imitate with her left arm the tremor of her right arm, her left arm also deviated inward. From time to time she exhibited tensions and tremor and something similar to clonus in her right foot, but at a given order she could produce a similar response in her left foot.

This case is one of hysteria which for psychogenic reasons has produced as isolated symptoms tremors in one arm and in one leg. The patient showed not only the tremor but also inward deviation of the arm which was afflicted with the tremor. Furthermore, it was possible to produce the same symptoms experimentally in the left arm. Investigations on normal subjects, furthermore, have shown that the attempt to imitate or to simulate tremor in the arm leads to inward deviation of the shaking arm.

SUMMARY AND CONCLUSION

When an arm is afflicted with hysterical tremor it shows a tendency to deviate toward the midline when the arm is stretched forward. If the other arm is not afflicted it may show a normal tendency to outward deviation. If both arms are afflicted the arms converge toward the midline. This convergence is due to adduction of the muscles in the shoulder girdle.

In cases of paralysis agitans, parkinsonism and alcoholism convergence of the outstretched arm may be found. However, this convergence is due to prevalence of the flexor muscles in the elbow. This flexion comes into appearance irrespective of whether one or both arms are extended. The divergence of the outstretched arms which is found in normal subjects is present also in patients with paralysis agitans. This divergence is due to outward movements in the shoulder girdle and comes into appearance only when both arms are stretched forward.

Case Reports

ASTROCYTOSIS ARACHNOIDEAE CEREBELLI

A Rare Manifestation of von Recklinghausen's Neurofibromatosis

A. Earl Walker, M.D., Chicago

Bizarre intracranial manifestations of von Recklinghausen's neurofibromatosis have been described frequently. The present case is a unique example of one of the peculiar lesions of this kaleidoscopic disease.

REPORT OF A CASE

R. N. L., a 16 year old girl, was admitted to the University of Chicago Clinics, to the service of Dr. A. Kenyon, on Aug. 6, 1939. She complained of severe headache during most of her life, aggravated recently and associated with nausea and vomiting, awkwardness and clumsiness for twelve years, urinary frequency and incontinence all her life and mental retardation.

The patient was an only child of parents who separated when she was 4 years old. Both parents were in good health, and the family history was irrelevant except that the patient's maternal aunt and grandmother had multiple small tumors all over their bodies (neurofibromatosis?). In her early teens the patient's head became so large that her mother was unable to get a hat to fit her. When 15 years of age she menstruated three times, but her periods then ceased. About the same time she became obese, weighing 138 pounds (62.7 Kg.), although she was only 5 feet ½ inch (151.5 cm.) in height. With thyroid medication her weight dropped to 120 pounds (54.4 Kg.).

The patient was well developed and somewhat obese, with a large head (hat size, 24, normal 21 to 22). Except for the moderate obesity, physical examination revealed no abnormalities. Her breasts were poorly developed. Her genitalia were normal. A few pigmented moles were present on the trunk and face and several larger café au lait spots on the abdomen and thighs, the largest measuring 7 by 3.5 mm.

She was well oriented and cooperated fairly well. Memory was poor, but not so defective that gross abnormalities were apparent in an ordinary conversation. Her intelligence quotient was 78 according to the revised Stanford Binet test.

Olfaction was apparently normal. Visual fields were slightly constricted concentrically; visual acuity in the right eye was 0.2 —1 and 0.2 in the left eye. Both fundi showed papilledema of about 2 D., with a small amount of exudate on each disk. The veins were engorged and tortuous. No hemorrhages were present. The pupils were 3 mm. in size and circular. They reacted sluggishly to direct light through a small range and better in accommodation. External ocular movements were full. At rest there was spontaneous nystagmus to the right; a coarse nystagmus appeared on looking to the right and a finer nystagmus on looking to the left.

There was a slight tremor in the finger to nose test, more pronounced sometimes on one and sometimes on the other side. The heel to knee test revealed unsteadiness on the right side. Rapidly alternating movements were slightly impaired on the right side. Sensation was normal throughout the body. All

From the Division of Neurosurgery of the University of Chicago.

tendon reflexes were lively. The plantar reflexes were extensor on both sides at times, but more constantly on the right.

The patient held the head stiffly, but passive movement was not resisted. She was unsteady on her feet and could not hop as well on the right leg as on the left. She was unable to walk tandem.

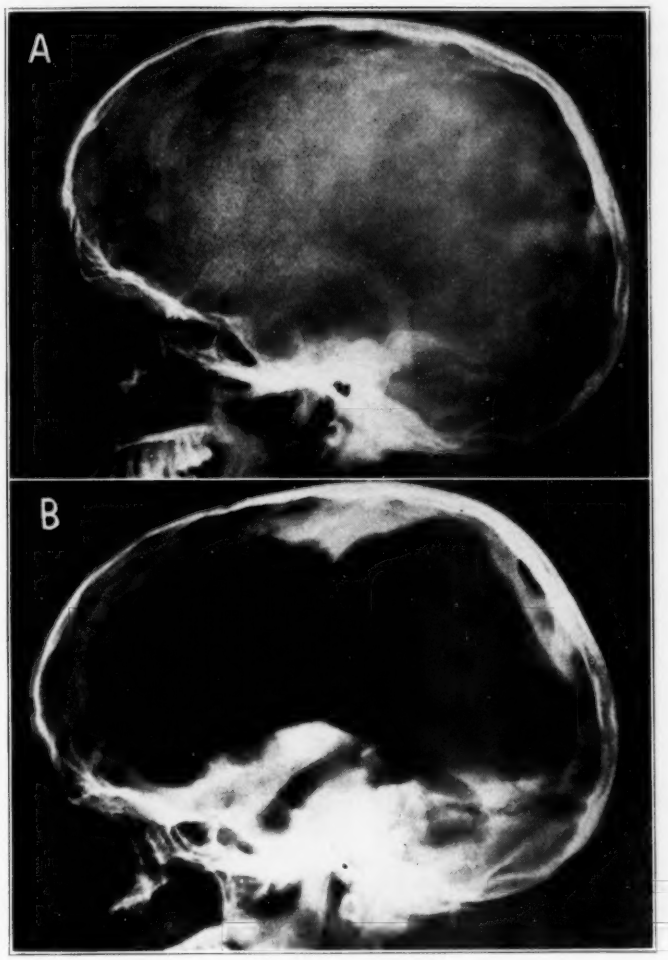

Fig. 1.—*A*, lateral roentgenogram of the skull, showing convolutional markings and the dilated sella turcica. *B*, lateral ventriculogram showing the marked hydrocephalus and the dilatation of the fourth ventricle.

Repeated urinalyses and examinations of the blood, including the Wassermann test, showed no abnormality. Her basal metabolic rate was —14 per cent. Roentgenograms of the skull revealed diastasis of the sutures and marked enlargement of the sella turcica. The optic foramens were normal (fig. 1 *A*).

Although a neoplasm in the third or fourth ventricles was suspected, the precise site and nature of the lesion were not apparent from the clinical and roentgenologic examinations; a ventriculogram, therefore, was made on August 16. This showed enormous hydrocephalus, the brain tissue being not over 1 to 2 cm. in thickness. The aqueduct of Sylvius and the fourth ventricle were dilated (fig. 1*B*). The films were interpreted as indicating an obstruction at the foramens of Luschka and Magendie.

After the ventriculographic procedure the patient suddenly stopped breathing. Artificial respiration and ventricular puncture resuscitated her, and her blood pressure returned to 130 systolic and 60 diastolic. Respirations, however, remained stertorous. She was immediately taken to the operating room, and with local anesthesia the posterior fossa was explored. When the dura mater was opened the right cerebellar hemisphere was seen to be firm and white. A large decompression, however, did not help, as the respirations continued to be stertorous, and the patient died about three hours later.

A complete postmortem examination, made by Dr. Eleanor M. Humphreys about an hour after death, showed recent operative wounds in the suboccipital region of the left ankle, small neurofibromas along the sympathetic nerves in the mediastinum and abdomen, neurinomatous proliferation in the appendix with periappendical adhesions, pigmented nevi and macules in the skin, atrophic and cystic changes in the ovaries and endometrium and atrophy of the thyroid gland. There were no abnormalities in the large nerve trunks.

Examination of the Brain.—There were small blood clots at the ventriculography wounds and about the suboccipital decompression. Blood was streaked over the left side of the pons. The interpeduncular space was filled with a thin blood clot. Hemorrhagic streaking extended over the base of the left frontal lobe and along the anterior part of the left sylvian fissure.

The dura mater in the middle fossae contained several nodules, 2 by 3 mm. in size. These were grayish, firm and attached to the outer surface of the dura mater. Each one lay in a little pit in the temporal bone of the floor of the middle fossa.

The cerebral hemispheres were large and soft. The cerebral convolutions were flattened. The entire right cerebellar hemisphere was smooth, hard and grayish white. The cerebellar folia could not be distinguished over the posteroinferior part of this hemisphere. Along the anterior and superior surfaces of the right cerebellar hemisphere the folial configuration was visible, although slightly obscured by the thickening of the arachnoid membrane. The vermis appeared normal. The right cerebellar tonsil was white and firm. The cerebellar hemispheres were about equal in size. There was a slight cerebellar pressure cone. The blood vessels of the circle of Willis appeared normal (fig. 2).

The entire ventricular system was enormously dilated, with numerous petechial hemorrhages over the ependymal surface. The right cerebellar hemisphere was hard and firm, but the folial markings stood out well on section and the dentate nucleus, normal in size and appearance, was readily distinguishable. The white matter of the cerebellum was grayish except for a narrow zone about the folia which had a normal white appearance. The gray color of the fibers entering the middle cerebellar peduncle was particularly striking. The lateral ventricles were about equally dilated and measured 15.3 cm. in the greatest anteroposterior diameter and 4 cm. in the greatest dorsoventral diameter. The cerebral cortex and underlying white matter were only 1 to 2 cm. in thickness. The third ventricle was 5.3 cm. in its greatest length and 3 cm. in its greatest depth. Several fenestrations

were present in the septum pellucidum. The cerebral aqueduct was about 3 mm. in diameter. The fourth ventricle measured 3.8 cm. in its greatest length and 2.8 cm. from the apex of its roof to the ventricular floor.

From the anterior surface of the right cerebellar tonsil a delicate fold of tissue swept down to the floor of the fourth ventricle, along which white glial streaks extended to the left lateral recess and seemed to occlude the foramen of Luschka. This foramen was small and communicated with a thin-walled arachnoid cave in the cerebellopontile angle containing choroid plexus. The pons and medulla were normal.

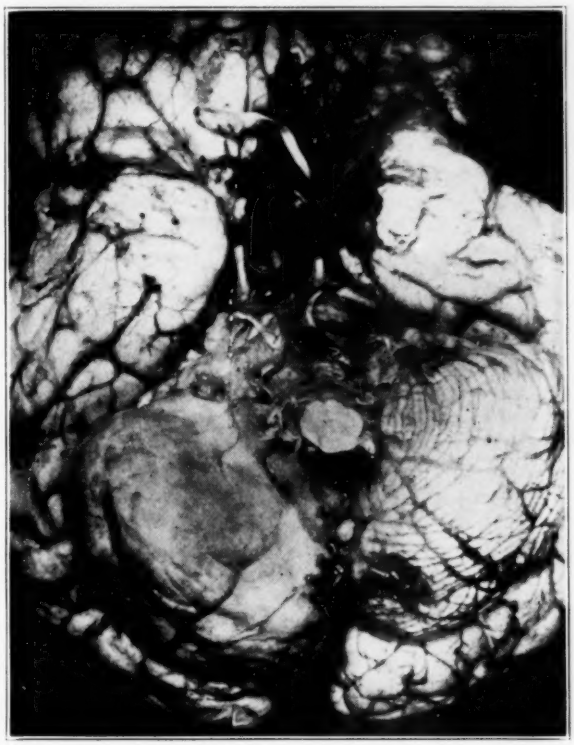

Fig. 2.—The base of the brain, showing the general appearance of the cerebellar hemispheres.

Blocks were taken from the right cerebellar hemisphere; some were embedded in pyroxylin and others cut with the freezing microtome. The appropriately cut sections were stained for cells with hematoxylin and eosin, thionine and phosphotungstic acid hematoxylin and for myelin by the Pal-Weigert and Smith-Quigley methods. Impregnations were made according to the following technics: the Bielschowsky silver method, the Globus modification of the Cajal gold chloride–mercury bichloride method and the fourth variant of Hortega, Bodian and Perdrau. Representative sections were taken from the cerebral cortex, the brain stem and the basal ganglia and stained by the Nissl and Smith-Quigley technics. The

peripheral nerves and nodules along the sympathetic nerves were embedded in pyroxylin and sections were stained with hematoxylin and eosin and by the Smith-Quigley method for myelin and were impregnated according to Bodian's technic.

Microscopic Examination.—The subarachnoid space over the right cerebellar hemisphere was filled with a mass of relatively acellular fibrous tissue (fig. 3). This mass filled the subarachnoid space between and over the folia of the cerebellum. It was thickest over the posteriorinferior surface of the cerebellum, but a thin sheet of the tissue was apparent over practically the entire hemisphere. The cells comprising this tissue had oval nuclei, somewhat larger than those of the granular layer of the cerebellum. The nuclear membrane was faintly distinguishable, and the nuclear material was pale staining except for several dispersed small chromatin granules. It was difficult to distinguish the cytoplasm of the cells, although in a few cells a small amount of faintly eosinophilic material surrounded the nucleus. Mitotic figures were not seen. Silver impregnations and the phosphotungstic acid hematoxylin stains showed medium-sized and fine fibers running from these cell bodies, usually in the direction of the folial sulcus but occasionally at right angles, thus forming a mat in the subarachnoid space (fig. 4). Between this mass of tissue in the subarachnoid space and the molecular layer of the cerebellum were fibrous bridges, which passed through the pia mater. Some penetrated about halfway through the molecular layer of the cerebellum. Frequently these bridges seemed to flow from a layer of cells just beneath the pia-arachnoid, and in places from a tangential or circular narrow layer of subpial fibers (fig. 5 *A*). These fibrous bridges at times were wide, occupying almost the entire side or summit of a folium, but usually were narrow, consisting of only ten to twenty fibers. Occasional glial nuclei were seen among the fibers. Perdrau preparations showed that the pia-arachnoid membrane was completely interrupted by these glial bridges (fig. 5 *C*). They demonstrated, moreover, rather marked proliferation of the arachnoid both over the surface and between the folia of the cerebellum (fig. 5 *C*). The glial bridges and the greater part of the subarachnoid fibrous tissue did not show impregnation for reticulin. There were a considerable number of thin-walled blood vessels in the subarachnoid mass. Although the cells in the subarachnoid space were poorly demonstrated by Globus' modification of Cajal's gold chloride—mercury bichloride method for impregnating astrocytes, the histologic appearance of the nuclei and the arrangement of the fibers identified them as fibrous astrocytes. The tissue in the subarachnoid space was, therefore, largely composed of fibrous astrocytes in a loose stroma of proliferated arachnoid membrane and a few blood vessels.

The folial pattern of the right cerebellar hemisphere was simple, and the complex branching normally seen was absent. The molecular layer of the cerebellum showed no abnormalities except for the occasional presence of a thin tangential outer fibrous layer, as already mentioned. The Purkinje cells were markedly decreased, being only about one-half to two-thirds as numerous as normal (figs. 3 and 5). The majority of these cells appeared normal, but the processes of some were swollen and distorted. Occasional empty baskets could be seen in the Purkinje layer. The granular layer was markedly thinned, being only about one-half as thick as normal (fig. 3). The individual granule cells, however, appeared normal.

The white matter of the right cerebellar hemisphere showed severe demyelination, only the U fibers staining well (fig. 6). There was a decrease of glia cells in the white matter, the majority being astrocytes rather than oligodendrocytes. Silver impregnations showed that the nerve fibers were markedly decreased, and many were fragmented or irregular. In the white matter of several folia were

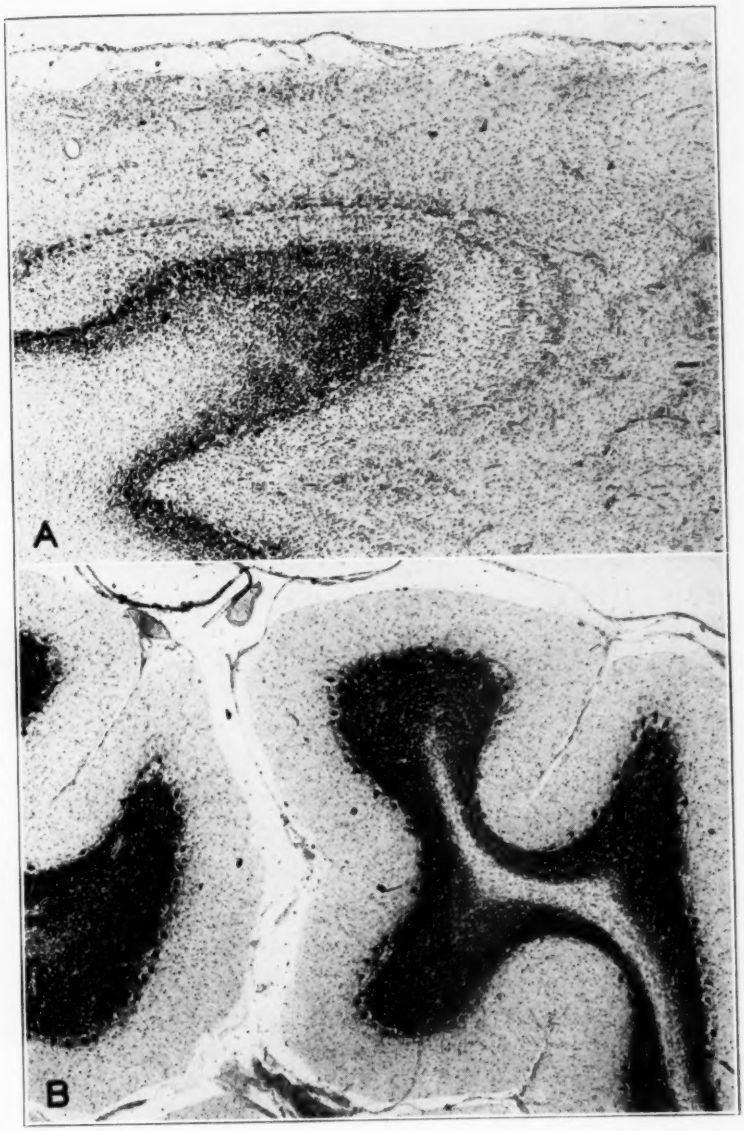

Fig. 3.—Photomicrographs of a folium: *A*, of the right cerebellar hemisphere; *B*, of the left (normal) hemisphere. The general appearance of the subarachnoid tissue and the parenchymatous cerebellar changes are evident. Thionine stain; × 30.

Fig. 4.—Glial bridges extending from the molecular layer of the cerebellum (below) to the glial tissue of the subarachnoid space. In *A* the bridges seem to originate from the molecular or the granular layers, and in *B*, from the superficial tangential fibrous layer, lying just beneath the pia mater. Phosphotungstic acid hematoxylin stain; *A*, × 220, *B*, × 310.

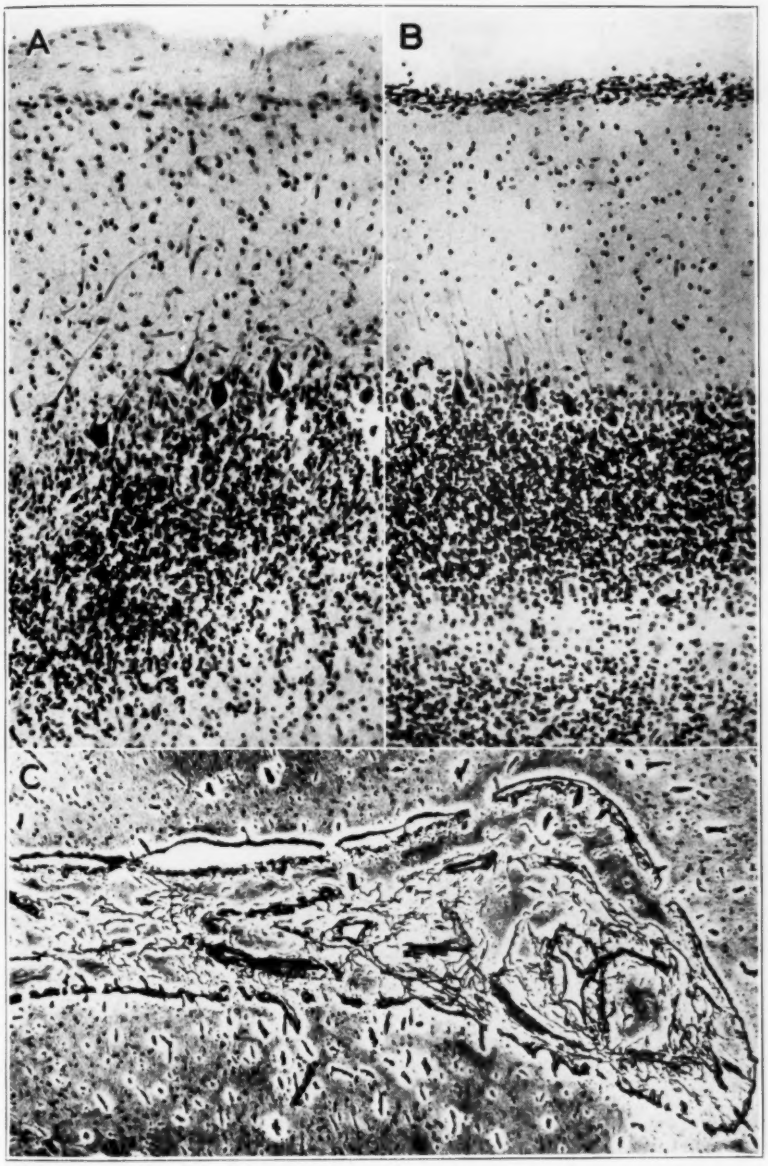

Fig. 5.—*A*, the cerebellar cortex, showing a thin zone of Obersteiner and a more superficial tangential fibrous layer. *B*, the cerebellar cortex of an infant, showing the normal appearance of the zone of Obersteiner. Thionine stain; × 120. *C*, a Perdrau preparation of the subarachnoid tissue, showing the arachnoid proliferation and the glial bridges interrupting the pia mater; × 65.

small calcospherites, usually descrete but occasionally clumped together. The opposite cerebellar hemisphere was normal.

In one small portion of the right cerebellar hemisphere was a cystic area, 5 to 6 mm. in diameter, containing a few thin trabeculae. These cysts were seen

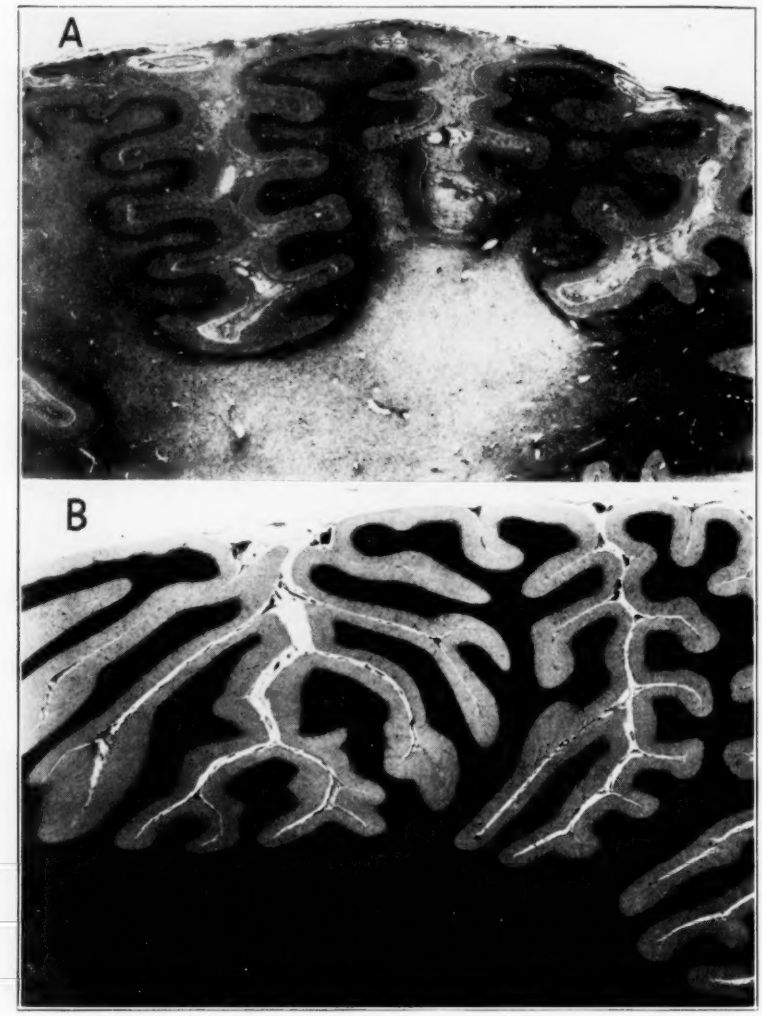

Fig. 6.—Sections stained for myelin: *A*, from the right, and *B*, from the left, cerebellar hemisphere. The simple folial pattern and the central demyelination of the right cerebellar hemisphere are prominent. Smith-Quigley technic; × 6.

to be lined by parallel layers of fibrous tissue containing sparsely arranged nuclei resembling those of astrocytes. Inside this lining was a thin layer of pink-staining, hyalin-like substance.

Running into the floor of the fourth ventricle from the subarachnoid space over the cerebellar tonsils, strands of fibrous tissue with a few nuclei formed a thin layer on the floor of the fourth ventricle just beneath a proliferated, thickened ependyma.

The pons showed no evidence of neoplastic involvement.

The cerebral cortex was thinned, and the neurons of the different layers were definitely decreased, although the cytoarchitectural structure was well preserved. The individual cells showed both chronic and acute changes—diffuse staining, swelling and fragmentation. Occasionally small perivascular hemorrhages were seen.

Sections of the tumors from the temporal fossa showed that they were glial nodules with a thin dural envelope, the inner fibers of which occasionally split and separated a small glial crescent. The cells of the nodule consisted largely of astrocytes and oligodendrocytes, no neurons being recognized.

COMMENT

A number of the pathologic features in this case require special consideration.

Infiltration of the Subarachnoid Space.—The extensive invasion by glial tissue of the subarachnoid space over the right cerebellar hemisphere was particularly marked over the inferior surface and tonsils of the cerebellum and slight over the superior surface. It is interesting that the vermis was practically uninvolved. The glial tissue thus involved essentially neocerebellar cortex, although the flocculus and the paraflocculus were implicated and strands passed across the fourth ventricle to the foramens of Luschka. The tissue in the subarachnoid space had no particular arrangement but was characterized by numerous fibers and few cell bodies. In areas the fibers lay parallel, but in many places they were irregularly matted.

The invasion of the subarachnoid space by neoplastic tissue is a common occurrence. The medulloblastomas (Bailey, Buchanan and Bucy [1]) frequently have extensive metastases in the subarachnoid space. Other malignant tumors, such as the sarcomas (Hsü [2]) and the glioblastomas, may spread widely by the spinal fluid channels. Dissemination by this means is less common in the slower-growing tumors, but oligodendrogliomas (Cairns and Russell [3]) and astrocytomas (Russell and Cairns [4]) rarely have small secondary growths in the subarachnoid space. Astrocytomas of the cerebellum not infrequently invade the subarachnoid space (Bergstrand,[5] Bucy and Gustafson [6]). Other glial

1. Bailey, P.; Buchanan, D. N., and Bucy, P. C.: Intracranial Tumors of Infancy and Childhood, Chicago, University of Chicago Press, 1939.

2. Hsü, Y. K.: Primary Intracranial Sarcomas, Arch. Neurol. & Psychiat. **43**:901-924 (May) 1940.

3. Cairns, H., and Russell, D. S.: Intracranial and Spinal Metastases in Gliomas of the Brain, Brain **54**:377-420, 1931.

4. Russell, D. S., and Cairns, H.: Spinal Metastases in a Case of Cerebral Glioma of the Type Known as Astrocytoma Fibrillare, J. Path. & Bact. **33**:383-391, 1930.

5. Bergstrand, H.: Weiteres über sogenannte Kleinhirnastrocytome, Virchows Arch. f. path. Anat. **299**:725-739, 1937.

6. Bucy, P. C., and Gustafson, W. A.: Structure, Nature and Classification of the Cerebellar Astrocytomas, Am. J. Cancer **35**:327-353, 1939.

tumors (Schuberth,[7] Harbitz,[8] Löwenberg[9]), the pathologic diagnosis of which is not definite, may infiltrate the subarachnoid space. In most instances a primary tumor of some size is present and the metastases are widespread, but in other cases, such as those of the diffuse sarcomatoses of the meninges, no focal growth is evident.

Glial Bridges.—Another outstanding characteristic is the glial bridges which extend from the molecular layer of the cerebellum to the tissue in the subarachnoid space. These bridges vary markedly in size, some being narrow and others wide. Some pass along with the blood vessels possibly in the Virchow-Robin space. They seem to spring from the molecular or the granular layer, although some of the bridges originate from a parallel layer of glial fibers which lie just within the pial margin of the folia (fig. 5*A*). This acellular glial layer does not seem to be the equivalent of the zone of Obersteiner, for in places a cellular layer (the zone of Obersteiner) lies deep to it (fig. 5*A*). In the normal cerebellum Cajal[10] has shown that the fibers of this layer are largely derived from glial cells of the deeper laminas. In the present case, in which the layer was much wider than in normal cerebellar folia, it is possible that the fibers originated from other sources, one of which may well be cells of the zone of Obersteiner.

Both glial bridges and the superficial fibrous layer have been described in association with cerebellar astrocytomas (Bergstrand,[5] Bucy and Gustafson[6]) and occasionally with other tumors (Oberling,[11] Bucy and Gustafson[6]). There seems to be no essential difference between the bridges in this case and those seen with cerebellar astrocytomas.

Parenchymatous Changes.—Besides the presence of a small amount of cystic astrocytomatous tissue in the cerebellar white matter, other pathologic changes are noteworthy. Although there does not appear to be definite widening of the cerebellar folia, such as is sometimes seen with cerebellar astrocytomas, the pattern of the folia is much simplified. Instead of having deep and branching sulci, a main fissure is present, with only a few small secondary sulci. The Purkinje cells are definitely decreased and show occasional degenerative alterations, such as empty baskets and swollen dendrites. The cells of the granular layer of the cerebellum are decreased in number. The demyelination of the white matter, leaving only a narrow zone of myelinated fibers along the granular layer, and the gliosis of the white matter are also striking pathologic changes (fig. 6). It is possible that the gliosis of the white

7. Schuberth, O.: Ueber diffuse Sarkomatose und Gliomatose in den Meningen des zentralen Nervensystems, Deutsche Ztschr. f. Nervenh. **93**:34-60, 1926.

8. Harbitz, F.: Ueber das gleichzeitige Auftreten multipler Neurofibrome und Gliome (Gliomatose), ("periphere und zentrale Neurofibromatose") auf erblicher Grundlage und mit diffuser Verbreitung in den Rückenmarks- und Gehirnhäuten, Acta path. et microbiol. Scandinav. **9**:359-405, 1932.

9. Löwenberg, W.: Ueber die diffuse Ausbreitung von Gliomen in den weichen Häuten des Zentralnervensystems, Virchows Arch. f. path. Anat. **230**:99-130, 1921.

10. Ramón y Cajal, S. R.: Histologie du système nerveux de l'homme et des vertébrés, Paris, A. Maloine, 1911, vols. 1 and 2.

11. Oberling, C.: La gliomatose méningo-encéphalique, Bull. et mém. Soc. anat. de Paris **94**:334-340, 1924.

matter represents merely a reaction to the demyelination and degeneration of nerve fibers.

Such parenchymatous alterations, however, are seen in the tissue about cerebellar astrocytomas (Bergstrand,[5] Bucy and Gustafson [6]) and have been stated by some to be due to compression by the tumor. In the present case there is, however, no reason to believe that local pressure was the main factor producing these parenchymatous changes, since the mass of the subarachnoid tissue was relatively small. Pressure resulting from the hydrocephalus should be the same on both cerebellar hemispheres, and were cellular atrophy the result of such pressure it should be present equally in the two hemispheres. Nor is there evidence that these parenchymatous changes might be the result of local ischemia due to infiltration of the tumor about the pial vessels, for areas of softening and necrosis were not present.

Other Pathologic Features.—The nodules, sometimes referred to as herniations, found on the outer surface of the dura mater which originally lay in small depressions in the floor of the middle fossa were seen microscopically to be composed of glial tissue enveloped in a dural capsule. Such herniations are not uncommon and have no pathologic significance (Brockbank [12]).

The marked dilatation of both lateral and the third and fourth ventricles was the result of narrowing or obliteration of the foramen of Magendie and both foramens of Luschka by the glial tissue. As a result of this hydrocephalus the cerebral cortex and underlying white matter showed degenerative changes.

Classification.—The nosologic designation of the cerebellar lesion in this case is not a simple problem. There seems to be no doubt that certain pathologic features are the result of a congenital malformation. The parenchymatous cerebellar abnormalities—the simple folial pattern, the decreased number of Purkinje cells, the narrowed granular layer and possibly the demyelination—are evidence of maldevelopment. That the subarachnoid tissue is also a congenital anomaly of the nature of a heterotopia is possible. However, the extent of this tissue in the subarachnoid space about the cerebellum and its infiltration about the fourth ventricle suggest that it should be regarded as a slow-growing tumor developing on the basis of a congenital malformation. The progressive symptomatology might also be interpreted as presumptive evidence of its neoplastic nature.

The tissue has many features in common with the astrocytomas of the cerebellum—cell type, fibrous glial bridges and parenchymal cerebellar alterations—which might lead to the conclusion that the lesion should be regarded as a small cerebellar astrocytoma with unusual and extensive subarachnoid growth. Such a classification would place the emphasis on what seems to be a relatively unimportant part of the lesion and on what, as mentioned previously, may be merely a reaction to demyelination and degeneration of nerve fibers.

Because of these nosologic difficulties, it seems advisable to classify this lesion simply as astrocytosis arachnoideae cerebelli, thus describing the predominant pathologic feature.

12. Brockbank, T. W.: Physiologic Herniations of the Brain, Arch. Neurol. & Psychiat. **20**:138-144 (July) 1928.

The peripheral manifestations of neurofibromatosis (beading of the thoracic and abdominal sympathetic nerves and cutaneous café au lait maculas) and cerebellar lesions are probably best considered as resulting from the same or similar congenital ectodermal abnormalities. The astrocytosis of the cerebellar meninges would then be a unique manifestation of von Recklinghausen's neurofibromatosis. The occurrence of gliomas in association with von Recklinghausen's neurofibromatosis is not uncommon (Bailey and Herrmann [13]), and several cases of extensive gliomatosis within the subarachnoid space of both the brain and the spinal cord have been reported (Schairer,[14] Schuberth,[7] Harbitz,[8] Löwenberg [9]). None of these cases resemble the present one, the neoplastic tissue being much more extensively disseminated.

SUMMARY

A 16 year old girl who had been unsteady on her feet for many years and exhibited evidences of hypopituitarism and cerebellar dysfunction died suddenly after a ventriculographic examination. Complete postmortem examination showed neurofibromas of the abdominal and thoracic sympathetic nerves and extensive astrocytosis of the meninges over the right cerebellar hemisphere. This glial overgrowth extended into the fourth ventricle, obstructing the foramens of Luschka and Magendie. Numerous glial bridges passed from the molecular layer of the cerebellum into the subarachnoid tissue. The Purkinje cells of the involved hemisphere were markedly decreased in number. The deep white matter was demyelinated, leaving only a thin layer of myelinated fibers about the base of each folium.

The pathologic changes in the cerebellum are considered to be on the basis of a congenital malformation and to be related etiologically to the peripheral neurofibromatosis.

13. Bailey, P., and Herrmann, J. D.: The Rôle of the Cells of Schwann in the Formation of Tumors of the Peripheral Nerves, Am. J. Path. **14**:1-37, 1938.

14. Schairer, E.: Ueber Neurofibromatose und ihre Beziehungen zu Gliomen und Hirnhernien, Ztschr. f. Krebsforsch. **40**:30-49, 1933.

DANGER OF SUBARACHNOID INJECTION OF ALCOHOL FOR RELIEF OF PAIN

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The purpose of this presentation is to point out a serious complication which may follow the injection of absolute alcohol into the spinal subarachnoid space when made in the region of the spinal cord.

REPORT OF A CASE

F. L., a man aged 61, was, so far as could be determined, in good health until he had coronary occlusion. After this incident attacks of anginal pain developed, which gradually incapacitated him. The pain started in the left side of the neck and radiated down the left arm and forearm and into the hand. Four years later, while in another state, he was advised to have an injection of alcohol into the spinal subarachnoid space for the relief of his pain. Within a period of minutes after the injection of alcohol spastic paralysis of the legs, partial paralysis of the arms and paralysis of the vesical and rectal sphincters developed. The entire body below the level of the injection became hyperalgetic.

These signs remained unchanged until he was admitted to the Graduate Hospital in Philadelphia, to the services of Dr. J. Howell and Dr. J. W. McConnell, one year after the injection of alcohol.

With the hope of relieving the pain by chordotomy, a laminectomy was performed. The fourth to the seventh cervical spinous processes and laminas, inclusive, were removed. The exposed dura did not appear abnormal, although it may have been slightly thickened. On opening the dura, the arachnoid on the left side of the dural sac was found to be as thick as the dura and densely adherent to the spinal cord. This arachnoid scar had caused pocketing of the cerebrospinal fluid. The spinal cord was markedly shrunken and showed almost complete obliteration of vascular markings over its surface. The excessive thickness of the arachnoid prevented the establishment of landmarks for the performance of a chordotomy.

The patient died of his cardiac disease about three weeks after operation. Permission for removal of the spinal cord, through the operative wound, was granted.

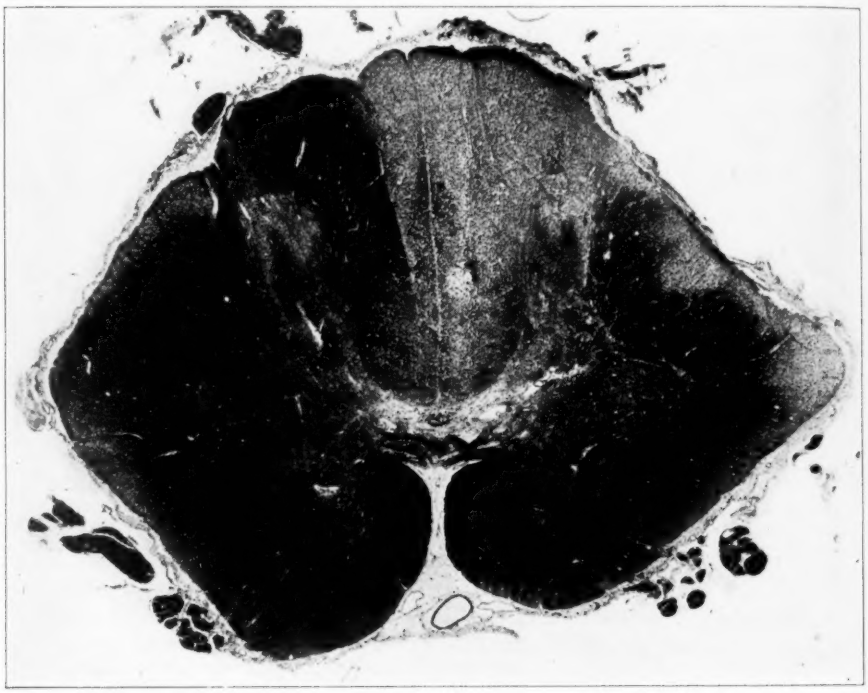
Sections were made through the seventh, fifth and third cervical segments. The lowest segment showed the severest lesion. At this level, the greater part of the tracts of Goll, the left column of Burdach and the adjacent posterior horn and root were completely demyelinated (figure). Only a small number of axis-cylinders were preserved. A dense glial scar replaced the parenchyma. In addition to this massive lesion, patchy degeneration was present in the anterior and posterior spinocerebellar tracts, in the marginal zone of the anterolateral tracts and in the pyramidal tracts. In the higher segments the degeneration of the posterior columns was about the same as that in the lowest segment studied, whereas the degeneration in the marginal zone was less pronounced. The pia was mildly thickened and

From the Department of Neurosurgery, the Graduate Hospital of the University of Pennsylvania.

scarred. The lowest section studied was not below the primary lesion. This conclusion was based on the fact that the degeneration of the posterior columns was still present and descending degeneration of the pyramidal tracts was not yet visible.

COMMENT

The importance of this observation is twofold. First, marked pathologic changes in the spinal cord were demonstrated after the injection of absolute alcohol into the spinal subarachnoid space. These changes were degenerative and involved both posterior columns, the left posterior horn, part of the periphery of the spinal cord and the pyramidal tracts.



Section through the lower cervical portion of the cord, showing severe degeneration in the posterior and anterior spinocerebellar, pyramidal and anterolateral tracts and in the posterior columns and horns following intraspinal injections of alcohol for relief of anginal pain.

Second, the clinical facts showed that in spite of the pathologic lesion produced, pain was not relieved. Relief of the anginal pain was slight. The threshold for pain was lowered over the entire body below the level of the injection. Even the pressure of bed sheets was annoying. It has been seen, in another case, that central pain in one leg, resulting from a thalamic vascular accident, became intolerable when the posterior columns of the spinal cord were blocked by spinal anesthesia.[1]

1. Frazier, C. H.; Lewy, F. H., and Rowe, S. N.: The Origin and Mechanism of Paroxysmal Neuralgic Pain and the Surgical Treatment of Central Pain, Brain **60**:44, 1937.

We wish to emphasize in consequence of this experience that alcohol should under no circumstances be injected intrathecally anywhere over the spinal cord. It should be used exclusively in the region of the cauda equina, if at all, and with all the precautions described by Dogliotti [2] and Stern.[3]

2. Dogliotti, A. M.: Nouvelle méthode thérapeutique pour les algies périphériques. Injection d'alcool dans l'espace sous arachnoïdien, Rev. neurol. **2**:485, 1931.

3. Stern, E. L.: Relief of Intractable Pain by the Intraspinal (Subarachnoid) Injection of Alcohol, Am. J. Surg. **25**:217, 1934.

News and Comment

COURSE OF INSTRUCTION IN THE RORSCHACH METHOD OF PERSONALITY STUDY AND CLINICAL DIAGNOSIS

The usual summer course of instruction in the technic of administering the Rorschach test and in scoring the responses will be offered by S. J. Beck, Ph.D., head of the psychology laboratory, department of neuropsychiatry, Michael Reese Hospital. The purpose of the course is to orient the student in interpretation, with especial emphasis on clinical classification. Records of responses as obtained from various healthy personality groups and from clinical groups (including patients with schizophrenia and some neuroses) will be scored, analyzed and interpreted. The primary aim of the course will be to demonstrate the test's practical application in investigating the whole personality, with particular reference to its clinical use.

The course will be in session in two two hour periods daily for five days, June 23 to 27, 1941, inclusive. Persons interested are invited to communicate with the medical librarian, Michael Reese Hospital, 2908 Ellis Avenue, Chicago, for further information.

CIVILIAN MENTAL HEALTH

The Military Mobilization Committee of the American Psychiatric Association has set up a subcommittee to deal with civilian mental health. Foremost among the problems under consideration is the matter of maintaining adequate psychiatric service for the civilian population. A number of psychiatrists have already been called out for the armed forces, and in addition a considerable amount of time is being devoted by psychiatrists in private practice to examination of men called under the Selective Service Act. It seems probable that the demands made by the armed forces will increase considerably.

Several approaches to this problem of maintaining adequate psychiatric service have been considered by the subcommittee. Among them is the further promotion of community psychiatry. Closer interaction with the social work agencies and other organizations in the community which are interested in social welfare together with further and intensified exploration of the field of community psychiatry may be reasonably expected to provide means of extending the activity of psychiatric personnel over wider groups.

COMMONWEALTH FUND FELLOWSHIPS IN PENAL PSYCHIATRY, 1941-1943

A fellowship in penal psychiatry in the University of Pennsylvania, provided by the Commonwealth Fund, is now available. The term of the fellowship is two years. The stipend is $2,400 the first year and $2,800 the second year. Minimal qualifications specify that the applicant be a graduate physician not older than 35, with an accredited internship and at least two years of acceptable psychiatric training. Inquiries should be addressed to Philip Q. Roche, M.D., secretary, Committee on Medico-Legal Fellowships, 255 South Seventeenth Street, Philadelphia.

CINCINNATI SOCIETY OF NEUROLOGY AND PSYCHIATRY

The Cincinnati Society of Neurology and Psychiatry has been organized, with the following officers: Dr. Thomas A. Ratliff, president; Dr. E. Armitage Baber, vice president, and Dr. Charles D. Aring, secretary-treasurer.

At the first scientific meeting, held at the University Club on Jan. 23, 1941, Dr. Charles D. Aring presented a paper entitled "Infectious Polyneuritis."

Obituaries

PAUL F. SCHILDER, M.D.
1886-1940

Paul Ferdinand Schilder, the son of Bertha Fuerth and Ferdinand Schilder, was born in Vienna on Feb. 15, 1886 and received his degree of Doctor of Medicine from the University of Vienna in 1909. He was assistant at the psychiatric clinic of the University of Halle from 1909 to 1912, under Anton, and assistant at the psychiatric clinic of the University of Leipzig from 1912 to 1914. He served in the Austrian army from 1914 to 1918, both at the front and at the base hospitals. He retained his interest in philosophic problems, studied intensively while in the army, often under heavy gunfire, and received his degree of Doctor of Philosophy from the University of Vienna in 1917.

He was assistant, and later first assistant, at the psychiatric clinic of the University of Vienna from 1918 to 1928, working with Wagner von Jauregg and Postal, and served on the medical faculty there from 1920 to 1929, being extraordinary professor from 1924 to 1928. During this time he was in personal contact with Freud and in close association with the Vienna Psychoanalytical Society.

He came to the United States in 1928 and was visiting lecturer at the Phipps Psychiatric Clinic of Johns Hopkins University from 1928 to 1930. In 1930 he was appointed to the staff of the Psychiatric Division of Bellevue Hospital as clinical director and was made research professor of psychiatry at New York University College of Medicine. He continued in these capacities until his untimely death, on Dec. 8, 1940.

Dr. Schilder had just left the Doctors Hospital, where he had visitied his wife, Dr. Lauretta Bender Schilder, and his 11 day old daughter, Jane, when he was struck by an automobile. He died a few hours later, without regaining consciousness.

Dr. Schilder was a Fellow of the American Medical Association, the American Psychiatric Association and the New York Academy of Medicine and a member of many other scientific societies, including the New York Neurological Society, the American Neurological Society, the New York Society for Clinical Psychiatry and the New York County Medical Society. He was one of the founders, and the first president, of the Society for Psychotherapy and Psychopathology.

Dr. Schilder approached the study of psychiatry from many angles. His philosophic training was utilized from one approach. His careful

studies in neuropathology (under Weichselbaum and Froheim) led to his constant attempt to link psyche with soma. In 1913, as a result of these studies, he published his classic description of encephalitis periaxialis diffusa, more commonly known as Schilder's disease, and this brought him international recognition when he was only 27 years of age. His studies of the psychoanalytic doctrine caused him to be sympathetic to the psychogenic approach to many types of disorders. He was an omnivorous reader, had a thorough knowledge of the literature of neuropsychiatry and associated subjects and was continually attempting new formulations.

Although Schilder belonged to the Vienna Psychoanalytical Society and for a time to the New York Psychoanalytical Society, he himself was never psychoanalyzed, and this brought him into controversy with the orthodox group of psychoanalysts. However, as a result of these controversies and discussions a broader and less rigid attitude toward psychoanalytic technics was given impetus. He introduced group psychoanalysis in the Bellevue Mental Hygiene Clinic and was one of the physicians responsible for short term psychoanalyses in selected cases.

A study of Dr. Schilder's bibliography since 1909 shows 248 publications, several of which are entire volumes. This bibliography is not complete, as it does not include any of his papers published in 1940 or those written but not yet published.

His interests were so all inclusive that any attempt to list them would sound like a psychiatric dictionary. He will probably be best remembered at New York University College of Medicine for his great interest in the students and his stimulating effect on them. As a result of his endeavors, a Psychological Club was organized among the students and speakers on psychiatry and allied subjects addressed the groups. In addition, voluntary courses dealing with various phases of psychiatry were given at lunch times and after school hours, and the students showed great enthusiasm for these courses.

Dr. Schilder is survived by his second wife and their 3 children, Michael, aged 3, Peter, aged 2, and his infant daughter, Jane, as well as by his mother and brother, who are living somewhere in occupied France.

Abstracts from Current Literature

Physiology and Biochemistry

THE EFFECT OF THE PITUITARY ADRENOCORTICOTROPIC HORMONE AND OF VARIOUS ADRENAL CORTICAL PRINCIPLES ON INSULIN HYPOGLYCEMIA AND LIVER GLYCOGEN. J. F. GRATTAN and H. JENSEN, J. Biol. Chem. **135**:511, 1940.

Previous evidence suggested that the anti-insulin effect of the anterior lobe of pituitary is attributable to the adrenocorticotropic principle in the gland and that injection of desoxycorticosterone acetate, in contrast to that of corticosterone acetate, did not produce a significant anti-insulin effect under the same experimental conditions. Further study has shown that the adrenal cortical principles corticosterone, 17-hydroxycorticosterone and 17-hydroxy-11-dehydrocorticosterone exert a pronounced anti-insulin effect and promote the deposition of glycogen in the liver. Desoxycorticosterone and various other steroids exert little or no effect on insulin hypoglycemia and formation of glycogen in the liver. It seems that only those adrenal cortical principles substituted in ring 3 (keto or hydroxy group) are principally involved in carbohydrate metabolism. The adrenocorticotropic factor of the pituitary produces a definite anti-insulin (glycotropic) effect and also promotes the formation of glycogen in the liver.

PAGE, Indianapolis.

THE EFFECT OF TESTOSTERONE PROPIONATE ON INDUCED CREATINURIA IN RATS. J. R. COFFMAN and F. C. KOCH, J. Biol. Chem. **135**:519, 1940.

In adult male rats which have been in a castrated condition for two months distinct creatinuria other than the insignificant and apparent creatinuria existing prior to operation does not develop. Daily injection of 900 micrograms of testosterone propionate caused an increase in body weight and a decrease in excretion of exogenous creatine. The gain in body weight and the decrease in creatinuria were greater in the castrated than in the normal animals. The castrated and normal animals react in a similar fashion to exogenous creatine and testosterone propionate. During administration of testosterone propionate and creatine the changes in the degree of creatinuria parallel the change in body weight until the body weight reaches a high level. At this level intense creatinuria reappears, even though administration of androgen is continued together with the ingestion of creatine. When the administration of androgen and creatine is discontinued, the degree of creatinuria falls to the insignificant values of the pretreatment level. The creatine content of muscles of normal and castrated rats with and without androgen treatment, but with a liberal supply of exogenous creatine, shows no significant difference. It would appear that the muscle tissue of the castrated rat is normal with respect to creatine content under the conditions of the experiment.

PAGE, Indianapolis.

THE EFFECT OF ALKALOSIS ON THE CHEMICAL COMPOSITION OF BRAIN, SKELETAL MUSCLE, LIVER AND HEART. HERMAN YANNET, J. Biol. Chem. **136**:265, 1940.

Alkalosis was produced by substituting bicarbonate for chloride without significantly altering the volume of body water. Since the concentration of sodium in the serum under these conditions remains relatively unchanged, the resulting alkalosis falls in the category of an alkali excess due to acid loss.

No significant changes in the water, nitrogen, chloride, sodium, potassium or phosphorus content were observed in the brain or skeletal muscle of cats kept in a state of alkalosis for twenty-four hours.

PAGE, Indianapolis.

HYPOTHALAMIC LESIONS AND PNEUMONIA IN CATS. E. W. HAERTIG and JULES H. MASSERMAN, J. Neurophysiol. **3**:293 (July) 1940.

Haertig and Masserman operated on 40 cats in three series. Bilaterally symmetric lesions were placed in the rostral (5 cats), the middle (26 cats) and the caudal (9 cats) region of the hypothalamus.

All animals with rostral lesions (anterior commissure to the optic chiasm) survived. Sixteen of the 19 animals with destruction in the middle region (chiasm into the mamillary bodies) succumbed to bilateral bronchopneumonia in one to eight days. Two of the 8 animals with caudal lesions (mamillary bodies and portions of the mesencephalon) died of pneumonia on the seventh day.

Animals with rostral lesions retained the ability to prevent an abnormal fall in body temperature; those with caudal lesions showed occasional disturbances of temperature regulation, whereas animals with lesions of the middle portion showed marked poikilothermia. All the animals responded to infection with fever, but those with lesions of the middle region of the hypothalamus could not maintain the hyperthermia in the presence of fluctuating environmental temperatures. A close correlation existed between the degree of poikilothermia and the incidence of pneumonia, but important exceptions occurred.

The following possible contributory factors were studied and found to have little or no etiologic significance in production of pneumonia in the animals with lesions of the middle hypothalamic region: distemper, anesthesia, basilar hemorrhage, peritonitis, aspiration, laryngeal obstruction, pulmonary emboli, gastrointestinal disturbances and exposure to extremes of temperature. Destruction of the central region of the hypothalamus therefore causes a high incidence of fatal pneumonia in cats, but the specific etiologic factors in this relationship require further investigation.

ALPERS, Philadelphia.

PROGRESSION MOVEMENTS ELICITED BY SUBTHALAMIC STIMULATION. WILLIAM H. WALLER, J. Neurophysiol. **3**:300 (July) 1940.

In cats anesthetized with pentobarbital sodium, alternating movements of the legs similar to those of normal walking and running were elicited by stimulation of the subthalamus in the region dorsal to the mamillary body with a 60 cycle alternating current. The sharp localization and low threshold of the response indicate that the subthalamus contains a specific center which directs the order of movement of the legs in locomotion.

ALPERS, Philadelphia.

INFLUENCE OF SENSORY SYSTEMS ON SPONTANEOUS ACTIVITY OF CEREBRAL CORTEX. F. H. LEWY and GEORGE D. GAMMON, J. Neurophysiol. **3**:388 (Sept.) 1940.

The activity of cortical brain cells in cats under deep anesthesia induced with pentobarbital sodium disappears on transection of the brain stem at the level of the colliculi, on destruction of the optic thalamus or on cutting the thalamocortical radiations. Removal of the cerebellum, the opposite hemisphere or the occipital or frontal pole does not abolish the discharge in the remaining cortex. Separation of the cortical connection to the thalamus, however, promptly stops the activity. These observations show that under anesthesia induced with pentobarbital sodium the spontaneous activity of the cortex is dependent on the integrity of the sensory pathways.

Stimulation of sensory nerves, of the thalamus or of thalamocortical fibers at rates between 6 and 20 per minute evokes, under this type of anesthesia, discharges which appear, both in pattern and in widespread distribution throughout the cortex, like the spontaneous bursts of activity. Stimulation at faster rates (16 to 20 per second) for one to five seconds sets up an after-discharge lasting several minutes. This also is widespread throughout the cortex.

These two lines of evidence show the importance of the sensory systems of the body in shaping the character of the continuous spontaneous activity of cortical brain cells.

ALPERS, Philadelphia.

AN ANALYSIS OF CORTICAL POTENTIALS MEDIATED BY THE CORPUS CALLOSUM. HOWARD J. CURTIS, J. Neurophysiol. **3**:414 (Sept.) 1940.

In cats under barbiturate anesthesia single electrical shocks applied to the cortex of one cerebral hemisphere evoke potentials at one or more points on the cortex of the other hemisphere. These responses are mediated by the corpus callosum. The potential wave is typically diphasic; it is composed of an initial surface positive component lasting about fifteen milliseconds and a surface negative component lasting about seventy-five milliseconds. If a convulsant drug, such as picrotoxin, is applied to the surface of the pia under the microelectrode, the negative component is greatly increased in magnitude and the positive component is slightly increased. If an anesthetic drug, such as pentobarbital sodium is applied, the negative component is completely obliterated but the positive component undergoes no change.

By inserting microelectrodes to various depths in the cortex and underlying white matter during the action of convulsant and narcotic drugs, it has been possible to gain some knowledge of the origin and course of the impulses which give rise to the potential changes recorded from the pial surface. The results indicate that the ascending fibers of the corpus collosum ramify in the upper layers of the cortex and end in the first layer, where they make synaptic connections with descending interneurons which lead to the deeper cortical layers. The ascending fibers give rise to the surface positive component of the wave and the descending internuncial fibers to the surface negative component.

ALPERS, Philadelphia.

FUNCTION OF MESENCEPHALIC ROOT OF THE FIFTH CRANIAL NERVE. KENDALL B. CORBIN and FRANK HARRISON, J. Neurophysiol. **3**:423 (Sept.) 1940.

With the Horsley-Clarke stereotaxic instrument for localization, action potentials in 20 cats have been picked up from the mesencephalic root of the fifth cranial nerve with a unipolar lead leading through a 5 stage, resistance-coupled amplifier with a differential input to a cathode ray oscillograph and loud speaker.

Action potentials, characteristic of proprioceptive impulses elsewhere, have been elicited from all portions of the mesencephalic root in response to opening of the jaw and thence stretch of the masticator muscles. Careful histologic study of the brain stems has demonstrated that this response was elicited only when the lead was within the homolateral mesencephalic root, never from surrounding neural structures or the contralateral root.

From the caudal half of the mesencephalic root action potentials have been elicited also from blunt pressure stimulation of the homolateral teeth and hard palate. In the cat, the canine teeth have been by far the most responsive of the oral structures.

The physiologic evidence here presented demonstrates the function of those mesencephalic root fibers found in degeneration experiments to enter the alveolar and palatine nerves. Impulses traversing these fibers to the motor nucleus are probably chiefly inhibitory, preventing damage to the structures concerned in biting (gums, teeth and hard palate). These impulses and those passing over the masticator nerves from the muscles of mastication, mediated by the mesencephalic root fibers, constitute the afferent limbs of masticator reflex arcs, thereby coordinating and controlling chewing movements.

No action potentials have been elicited from the mesencephalic root of the fifth nerve or from the third, fourth or sixth nerve as the result of stretch of the extrinsic ocular muscles. The authors realize that this evidence does not exclude the mesencephalic root from a role in the sensory innervation of the ocular muscles.

No evidence has been obtained to support the assertion by other workers that the mesencephalic nucleus gives rise to cranial autonomic fibers passing to muscles of the face and tongue. On the contrary, evidence is presented which indicates that an autonomic function for mesencephalic root fibers is highly improbable.

ALPERS, Philadelphia.

Neuropathology

THE ANGIOBLASTIC GROUP OF MENINGIOMAS: A STUDY OF THIRTEEN VERIFIED CASES. CYRIL B. COURVILLE and KENNETH H. ABBOTT, Bull. Los Angeles Neurol. Soc. **5**:47 (April) 1940.

In reporting 13 cases of angioblastic meningioma, Courville and Abbott direct particular attention to the histologic varieties of this group of tumors and discuss their classification and relation to other meningiomas. The 13 tumors were divided into four types: 1. Meningeal angioblastomas, 3. These tumors contained many capillary spaces in a poorly cellular stroma with a network of reticulin, and seemed to correspond to the cerebellar hemangioblastomas. 2. Transitional angioblastomas, 3. Portions of these tumors resembled those of the first type, while others showed solid cellular areas suggesting the meningotheliomatous meningiomas. These tumors seemed, therefore, to occupy a position intermediate between the two types. 3. Angioblastic meningiomas, 4. These were richly cellular tumors, with large blood spaces lined by a single endothelial layer of tumor cells and surrounded by a network of reticulin. The identity of the cells of these tumors with those of the mesothelial type is not certain. 4. Combined meningotheliomatous-angioblastic meningiomas, 3. In these tumors there was a mixture of syncytial or meningothelial tissue with tissues resembling those seen in angiomatous types 2 and 3. Courville and Abbott place special emphasis on this type as being a form of meningioma not heretofore delineated by others. In discussing the general classification of the meningiomas, the authors state that the primitive mesenchymal meningiomas are apparently rare and have not come under their personal observation in an examination of over 100 meningiomas. They recognize fibroblastic mesothelial and angioblastic (their type 1) forms, with one transitional variety combining mesothelial and angioblastic elements. Perhaps their types 2 and 3 are intermediate between types 1 and 4. Combinations of fibroblastic and angioblastic meningiomas apparently do not occur. MACKAY, Chicago.

INVOLVEMENT OF THE NERVOUS SYSTEM IN SICKLE CELL ANEMIA. J. G. HUGHES, L. W. DIGGS and C. E. GILLESPIE, J. Pediat. **17**:166 (Aug.) 1940.

Hughes and his collaborators present 6 cases of sickle cell anemia with cerebral complications, review the literature and discuss the pathologic changes. From the records of their cases and from 25 others culled from the literature it seems that neurologic manifestations are frequent, the lesions are multiple and the location of the lesions is variable. The onset of symptoms is often sudden and extensive enough to cause grave manifestations, such as convulsions, meningeal signs, pains, aphasia, paralyses, coma and death. The prognosis following lesions of the central nervous system is poor, varies widely and is unpredictable. Frequently there are patients who have recurrent episodes in which the symptoms and signs are referable to the nervous system. In these cases there is a tendency for the later attacks to be more severe. The cerebrospinal fluid observations are variable and often normal, although the patient has definite neurologic signs. Fluids which on first examination were normal may later become abnormal. The abnormalities of the cerebrospinal fluid consist of increased pressure, presence of sickle cells, xanthochromia and increase in protein and leukocytes. The cerebral lesions are varied and widespread. It is the authors' opinion that the lesions of the central nervous system are primarily intravascular. The most common changes found at necropsy are dilatation of peripheral blood vessels and congestion with sickle-like erythrocytes. Multiple thrombosis of smaller blood vessels in the same area is the rule. Other vascular lesions in the small vessels include infiltrative and degenerative changes in the vessel walls, perivascular edema, cellular exudation, hemorrhage and necrosis. The changes in the larger arteries and arterioles include intimal proliferation, fragmentation and reduplication of the intima, medial fibrosis and hyalinization, and sometimes hemorrhage into the media, with pigmentary changes and calcification. The convolutional gray matter and, to a less extent, the white matter

adjacent to it are involved. The spinal cord has been studied inadequately, but the meager evidence available reveals meningeal and vascular lesions and degenerative changes in ganglion cells comparable with those found in the cerebral cortex. The presence of elongated and multipointed sickle-like erythrocytes, the increase of leukocytes, nucleated red blood cells, macrocytes and platelets and in some cases the venous back pressure, due to obliterative changes in the arterioles of the lung and myocardial failure, increase the normally slow blood flow through the small vascular channels of the cortex. The arterial changes are interpreted as secondary to capillary and venous thrombosis. The pathologic observations correlate well with the clinical manifestations. The milder symptoms (headache, drowsiness, dizziness, minor meningeal irritations and temporary sensory and motor symptoms and signs) are probably explainable on the basis of vascular stasis and small thrombi with good collateral circulation. Confusion psychoses, mental changes, convulsions, aphasia, hemiplegia, paresthesias, delirium and coma may occur with more extensive lesions. Dilated vessels, occasional hemorrhages, edema of the fundi, localized facial swelling, dilated and thickened and tortuous temporal vessels, bulging fontanels and relief of headache following epistaxis indicate that cerebral stasis is present. The severe joint and osseous pains complained of commonly are probably due to vascular lesions, inflammatory reaction and irritation of nerve endings in these tissues. Some severe pains in the back and stiffness of the neck interpreted as meningeal may be articular in origin or due to lesions in tendons and muscles. Severe pains in the chest and abdomen and pains in the skin and extremities in some cases are probably referred pains which are primary in the central nervous system or spinal ganglia. There is no specific therapy.

J. A. M. A.

CLINICOANATOMIC STUDY OF A CASE OF SYDENHAM'S CHOREA. M.-T. CALLEWAERT, J. belge de neurol. et de psychiat. **40**:5 (Jan.) 1940.

Callewaert states that there is as yet no conclusive opinion regarding the nature of the pathologic changes in Sydenham's chorea. Some authors believe the process to be inflammatory, while others regard it as purely degenerative. In an attempt to clarify the matter, she presents the clinical and pathologic report of the case of a 15 year old girl in whom chorea developed in association with acute rheumatic fever and endocarditis. The outstanding pathologic changes in the nervous system were as follows: There was intense, generalized congestion of the brain, most marked in the hypothalamus, the periventricular area and the corpus striatum, and also in the cerebral and the cerebellar cortex. There were small hemorrhagic areas in the cerebral peduncles and the substantia nigra. There was no cellular infiltration in the perivascular spaces. There was a mild subcortical glial reaction in the white matter of the cerebrum and cerebellum. There were degenerative changes in the small cells of the caudate nucleus and putamen, the hypothalamic region, the red nucleus, the subthalamic nucleus and the amygdaloid nucleus, and less marked changes in the rolandic cortex, the dentate nucleus and the reticular substance in the medulla. In these same areas there was moderate glial infiltration. Callewaert states that these cellular alterations together with the glial reaction, are degenerative. It is possible that the intense congestion and the hemorrhagic changes are inflammatory, but she believes them also to be degenerative.

The author regards Sydenham's chorea as a toxic-infectious process in which the toxic element is largely predominant. When they exist, inflammatory lesions are always moderate, discrete, well localized and associated with degenerative changes. The differentiation between the changes which suggest inflammation and those characteristic of degeneration are too minimal to indicate two types of chorea. The variations observed in individual cases are probably indicative of the degree of virulence of the disease in its acute stages or of the individual reaction to the etiologic process.

DE JONG, Ann Arbor, Mich.

PERIARTERITIS NODOSA AND DIFFUSE SCLEROSIS. J. BALÓ, J. belge de neurol. et de psychiat. **40**:160 (March) 1940.

Various types of cerebral involvement have been described in cases of periarteritis nodosa, and in all instances it has been felt that vascular lesions were responsible for the cerebral changes. Baló is of the opinion that the cerebral alterations in his case were independent of the vascular lesions. He reports the case of a 23 year old locksmith, who first complained of pain in the legs and difficulty in walking. He had marked ataxia, inequality of pupils, nystagmus and optic neuritis. Albuminuria later developed, and he passed into coma and died. Postmortem examination showed periarteritis nodosa, with some involvement of the cerebral vessels, but the outstanding change observed in examination of the nervous system consisted of disseminated softening and demyelination of the white matter, both in the brain and in the spinal cord, with hypertrophy of the neuroglia. The changes were characteristic of diffuse or disseminated sclerosis.

Often in periarteritis nodosa there is degeneration of the peripheral nerves, manifest as polyneuritis, and this is thought by many to be due to involvement of the arteries supplying the individual nerves. Baló believes, however, that the process may be toxic, and that the changes in the central nervous system in his case were definitely of toxic origin. Associated with periarteritis nodosa are areas of necrosis in the pancreas, liberating lecithinolytic ferments whch cause the degenerative changes in the peripheral nerves, and in certain instances in the central nervous system as well.

DE JONG, Ann Arbor, Mich.

PATHOGENESIS OF PLAQUES IN MULTIPLE SCLEROSIS. G. DÖRING, Deutsche Ztschr. f. Nervenh. **150**:146, 1940.

This article is devoted to a consideration of the problem whether the "noxious agent" of multiple sclerosis spreads from the spinal fluid or from the blood vessels. In favor of the former hypothesis is the fact that plaques are common in the vicinity of the ventricles and over the surface of the pons and spinal cord. Earlier investigators have pointed out, however, that the lesions of the acute form of multiple sclerosis have a close relation to the vascular apparatus. The present survey of several specimens, cut in serial sections, indicates that this is true of many of the older plaques also, as has been demonstrated by Falkiewicz and others. Even the subependymal plaques are often evidently of this type; they may follow the periventricular veins, and a layer of preserved myelin may often be formed between the ventricle and the plaque. These cannot be due to stasis following venous obstruction, first, because it is not clear that all of them occur about veins and, second, because it is obvious that any thrombi in the vicinity of lesions are due to the inflammatory process. This cannot be emphasized too often. The correspondence of many plaques with the course of large vessels shows that the myelinolytic agent escapes from the vascular system.

PUTNAM, New York.

THE HYPOTHALAMUS IN OBESITY. W. RITTER, Frankfurt. Ztschr. f. Path. **52**: 149, 1938.

The hypothalamus, including the hypophysis, was examined in 4 instances, respectively, of constitutional obesity, Morgagni's syndrome (thick skull and bony excrescences of the inner surface of the frontal bone), Cushing's syndrome and cerebral polyglobulism (Günther). No noteworthy changes were demonstrable. However, in all 4 instances there were marked basophilia of the hypophysis and an increase of the lipoid content of the adrenal cortex. The author regards the changes in the hypophysis as compensatory, brought about by an interference in the balance of the endocrine organs which control fat metabolism. He compares the hypophysial changes with the hyperplasia or adenoma in the parathyroids in certain diseases of the bones.

SAPHIR, Detroit. [ARCH. PATH.]

EXTRAPYRAMIDAL MOTOR SYSTEM: I. A CASE OF HEMICHOREA ASSOCIATED WITH A FOCAL LESION OF THE STRIATUM. E. GRÜNTHAL and K. HARTMANN, Monatschr. f. Psychiat. u. Neurol. **102**:107, 1940.

Grünthal and Hartmann report a case of hemichorea associated with a focal lesion of the caudate nucleus. In the patient, a man aged 74, there suddenly developed choreic movements affecting the muscles of the left side of the face, the left upper extremity and, to a lesser extent, the right upper extremity. Marked improvement occurred within two months. He was observed a year later, at which time he exhibited choreiform movements of the facial muscles bilaterally and the left upper and lower extremities. The tendon reflexes were diminished, but there was no disturbance of muscle tone. The patient soon became stuporous and died in a few days. Postmortem examination disclosed a carcinoma of the esophagus with metastases to the lungs. In the brain a focus of incomplete softening was noted immediately under the ependyma which covered the head of the right caudate nucleus. The lesion involved about one third or one fourth of this structure, which also showed a few perivascular foci of devastation. Three small areas of softening were located in the adjacent white matter, one of them extending into the basal portion of the head of the caudate nucleus. Several small acellular areas were encountered in the cortex of the right frontal lobe and insula; these changes were regarded as too slight to be of any significance. The case presented features which lend support to Jakob's belief that the striatum innervates both sides of the body, with emphasis on the contralateral side. Apparently bilateral symptoms occur when the process is acute, the ipsilateral disturbances disappearing in the further course of the disorder. The observations suggest, in agreement with certain others in the literature, that the head of the caudate nucleus contains centers which influence the whole body. This is contrary to a previously expressed theory that functions concerned with speech, facial movements and the arms, trunk and lower extremities are represented, in the order named, in a rostral to a caudal direction in the striatum. There was no evidence of damage to the fibers which run from the thalamus to the caudate nucleus, though some workers have claimed that interruption of these fibers plays a leading role in the origin of chorea. Knowledge of the extrapyramidal system is very incomplete, but it does not seem likely that choreic disturbances can be explained in a uniform manner from the viewpoint of localization or pathologic physiology. The motor system can react to damage in only a limited number of ways, and it is probable that chorea is a form of motor reaction which arises under a variety of circumstances.

ROTHSCHILD, Foxborough, Mass.

HISTOPATHOGENESIS OF CEREBRAL APOPLEXY IN CASES OF HYPERTENSION. I. SCHEINKER, Monatschr. f. Psychiat. u. Neurol. **102**:158, 1940.

Scheinker reports a case of hypertension in which a cerebral hemorrhage occurred as a terminal event. The illness was characterized by an intermittent course of ten years' duration, with epileptiform attacks, variable focal neurologic phenomena and mental disturbances. Microscopic examination of the brain disclosed numerous small areas of destruction and traces of old hemorrhagic foci in the neighborhood of the fresh extravasation of blood. Miliary foci of softening were scattered throughout the other parts of the brain. The small vessels of the meninges and cerebral substance showed severe hyaline changes. According to Scheinker, this type of vascular lesion does not belong in the sphere of general arteriosclerosis but is identical with the hyaline degeneration of the small renal vessels associated with chronic hypertension. Involvement of the vessels probably impairs their ability to react to vasomotor stimuli, and sudden changes of blood pressure may produce alterations in the permeability of the walls, leading to extravasation of blood. Rapid and widespread dissolution of the surrounding tissues occurs because they have already been damaged by chronic insufficiency of the blood flow. It seems likely that the structural alterations of the vessel walls are preceded by functional disturbances in which angiospastic phenomena

are prominent features. Thus, hyaline degeneration of the small cerebral vessels is the gross organic end stage of a pathologic process that begins as a functional angiospastic disorder. A well defined clinical syndrome results from this disorder, which apparently represents a special type of reaction to a variety of noxae.

ROTHSCHILD, Foxborough, Mass.

Psychiatry and Psychopathology

LIBIDO AND REALITY IN MASOCHISM. BERNHARD BERLINER, Psychoanalyt. Quart. **9**:322, 1940.

The current explanations of the psychodynamics of masochism—suppression of aggression by turning the impulse against the self and projecting the aggression onto an external object because of fear of aggression, expression of the death instinct and a desire for punishment because of guilt—are not entirely satisfactory. Berliner believes that the basis of masochism lies in the patient's need to be loved by a hostile person.

Masochistic persons seem to have an erotization of the whole body surface and need a close bodily contact or an intimate personal relation with others. This need to be loved is in conflict with external reality—a reality which the patient falsifies into a hostile one by projection or provokes and manipulates into providing him with suffering and frustrations. According to the history, such a person has been an unloved, hated and mistreated child, and frequently the rejecting parents have hidden their rejection under the guise of overprotection. The patient when a little child does not realize that the persons whose love he desires really hate him because he has no knowledge of any different kind of love. In order to be loved he tries to adapt himself to the hating love object, tries to be the type of child he is supposed to be and so develops into a hate object for the environment. In doing this he identifies his superego with the primarily hostile parent. The identification occurs not in substituting a lost gratification after the loss of a love object but in attempting to preserve the love object and to prevent its loss. The masochistic ego introjects the hating object in order to save it as a love object.

Later the child refuses to recognize the fact that the person whom he thought loved him really hated him. For the sake of love he represses his own reaction of hate because he was not loved, his feeling of being harmed and his perception of the unkindness of others and solves the conflict by turning his hate against himself in conformity with the real hate toward his infantile love object. Aggressive impulses and guilt feelings are not as important in the psychodynamics of masochism as is the impulse to seek love from primarily hating parents. This enables a masochist overreadily to accept castration because his adjustment depends on the repression of the perception of injuries through his need for love and on the repression of his awareness that he accepts suffering as a substitute for love because he at one time suffered constantly at the hands of a person he loved. The hatred as a reaction to his rejection is repressed and appears as an undertone of accusation in his suffering and complaining. The patient accepts the hostility of his superego because it is the same as the hostility of his love object, and he may even treat others cruelly because that is his way of loving. In brief, "the masochist dreams loving souls into those people who hate him."

PEARSON, Philadelphia.

EFFECT OF REPRESSION ON THE SOMATIC EXPRESSION OF EMOTION. J. EISENBUD, Psychosom. Med. **1**:376 (July) 1939.

Eisenbud utilizes the method originally devised by Luria and previously used by himself in which a "complex" is artificially introduced during the deep stage of hypnosis and then "repressed" by means of posthypnotic amnesia. Although quantitatively inaccurate in an absolute sense, this method affords an opportunity for a relatively reliable determination of the postulated relation between the

degree of repression and the degree of parasympathetic excitation. The latter is measured objectively by recording the gastric motility and secretory rate of the parotid gland of a patient in whom control readings have established the subject's natural gastric motility.

On the basis of a number of experimental sessions with an 18 year old girl, Eisenbud concludes that artificially induced repression appears to be temporally associated with evidence of parasympathetic excitement. The specific causal relationship existing between the psychic manifestation of repression and the somatic manifestation of parasympathetic excitation remains undecided.

SCHLEZINGER, Philadelphia.

CONDITIONING NEUROSES IN DOG AND CAT. S. DWORKIN, Psychosom. Med. **1**:388 (July) 1939.

Dworkin lists the known etiologic factors concerned in the production of neuroses in animals as follows: (1) undue strain on the nervous system; (2) constitutional susceptibility; (3) castration (in the male), and (4) suppression of neuromuscular activity. In reviewing his experiments in conditioning dogs and cats to tone discriminations and hearing thresholds, Dworkin was able to confirm the etiologic significance of neuromuscular suppression. In his experiments with dogs the Pavlov procedure of restraint in harness was followed, while in the experiments with cats a small cage allowing ordinary body movements was used. Neurotic behavior occurred eventually in most of the dogs and was major in character, while in the cats disturbances were seldom noted and were comparatively simple. In the tone-discriminating experiments 2 dogs manifested a mixed inhibitory and excitatory neurosis characterized by an increasing tendency to reject food associated with marked psychomotor activity; the cats responded with simple disinhibition in the form of positive reactions to both positive and negative stimuli. In the auditory threshold experiments 4 dogs showed an unusual inhibitory neurosis characterized by posturing and absence of orienting reaction; the cats showed variable behavior disturbances characterized chiefly by excitation and usually complete disinhibition. These experiments seem to show that the quiet, restrained dog manifests severe neurotic alterations, while the comparatively free moving cat shows relatively minor derangement. Further direct experiments are necessary to decide whether the restraint in dogs used in these experiments was primarily an inherent species characteristic or the effect of restraint in harness. In any case it may be concluded that freedom of locomotion determines the character of the neurotic disturbance in animals.

SCHLEZINGER, Philadelphia.

ALCOHOL: A STUDY OF SOCIAL AMBIVALENCE. ABRAHAM MYERSON, Quart. J. Studies on Alcohol **1**:13 (June) 1940.

Man is a study in contrasts. On the one hand he cultivates hedonism and on the other asceticism. The same attitude holds toward the problem of sex. On the one hand man extols the sexual situation and on the other denounces it. So, too, with the use of alcohol; it is extolled by some and condemned by others. Myerson questions the assertion that the alcoholic person drinks in order to escape from his neurosis. He points out that among Jews, where there is much frustration and neurosis, the abuse of alcohol is universally condemned and an escape into alcoholism is rare. Myerson denies that excessive drinking derives from neurosis, psychosis or conflict. "Men drink in celebration as well as for relief. They drink to lend ceremony, color and fellowship to life, just as surely as to banish anxiety, dread and frustration. They drink out of recklessness and abandon which is not at all necessarily a compensation for an inherent caution and fatigue of spirit. The drink, too, because the inhibitions of life seem at times ridiculous and often alcohol represents not an escape but a revolt against the overstressed, perhaps necessary caution, decorum, and orderliness of existence."

ALPERS, Philadelphia.

Vegetative and Endocrine Systems

HISTOLOGIC CHANGES IN THE PITUITARIES OF PARABIOTIC RATS. ISOLDE T. ZECKWER, Arch. Path. **30**:461 (July) 1940.

The pituitaries of female rats united in parabiosis with ovariectomized rats showed degranulation of basophils and, in some instances, moderate degranulation of acidophils during the intervals of time studied. Extreme degranulation occurred after a year. The pituitaries of male rats united in parabiosis with gonadectomized rats showed only occasional very slight degranulation of basophils. The pituitaries of rats united in parabiosis with thyroidectomized rats showed no conspicuous changes. After gonadectomized rats were united in parabiosis with thyroidectomized rats, castration cells were found similar to those occurring in single rats. Thyroidectomy cells persisted except in the case of 1 female, maintained for one hundred and eighty-nine days, which showed the usual effects of degranulation by estrogen in very large doses.

WINKELMAN, Philadelphia.

THE RELATION OF THE ANTERIOR PITUITARY TO BILE PRODUCTION. O. B. HOUCHLIN and C. W. TURNER, Endocrinology **26**:821 (May) 1940.

Houchlin and Turner report on the effect of injections of anterior pituitary on bile secretion in anesthetized guinea pigs. The average hourly production of bile in 7 normal female animals of standard weight (between 280 and 370 Gm.) at a definite time of day and under anesthesia induced by avertin with amylene hydrate and ether was found to be 2.94 cc. After the injection of 25 mg. of an initial extract of the anterior lobe of the pituitary gland there was a rise in secretion of bile extending from four to eight hours. The average hourly production of bile of 14 animals given injections of the extract was 5.45 cc., an increase of about 85 per cent. This definite increase in bile secretion is taken as indirect evidence that the secretion of the anterior lobe of the pituitary is also concerned in the rate of fat absorption from the intestine and that in the normal animal it is probable that the ingestion of fat stimulates the discharge into the blood, either by nervous or by chemical means, of the anterior pituitary factor, which then influences fat metabolism, including the production of bile and the rapid absorption of fat.

PALMER, Philadelphia.

EXPERIMENTAL STUDIES OF THE ANTERIOR PITUITARY. M. SCHWEIZER, H. A. CHARIPPER and W. KLEINBURG, Endocrinology **26**:979 (June) 1940.

In previous articles, the authors have pointed out that tissue of the anterior lobe of the pituitary homoplastically transplanted into the anterior chamber of the eye of the hypophysectomized female guinea pig apparently secretes only follicle-stimulating hormone, as evidenced by the fact that the ovarian follicles are well maintained and liberate sufficient estrogenic hormone to produce enlarged uteri and prolonged estrous openings of the vagina. However, the follicles fail to reach maximum size, and neither ovulation nor formation of luteal tissue occurs; therefore it may be assumed that such transplants or implants do not secrete a luteinizing hormone.

In extending their experiments to the hypophysectomized male, the authors have found that the grafts maintain the androgenic as well as the spermatogenic activity of the testis. The sex difference in the implants apparently played no part, as the effects of pituitary from male and female donors were indistinguishable. The occurrence of all stages of spermatogenesis in the testes and the presence of motile sperm in the ejaculates are indicative of the maintenance and normal functioning of the germinal epithelium, and although the interstitial tissue of the testis was less abundant than that in the normal animal, the individual cells of this tissue were normal in appearance. There was definite evidence of androgenic activity in the large size and distended state of the seminal vesicles, the size of horny styles and the positive results of the electrical ejaculation tests.

PALMER, Philadelphia.

A Subclinical Endocrinopathy as a Factor in Autarcesiologic Susceptibility to Poliomyelitis. W. L. Aycock, Endocrinology **27**:49 (July) 1940.

Aycock describes two series of experiments which suggest a faulty economy of estrogenic substance as a cause of the apparent autarcesiologic susceptibility to poliomyelitis. In the first experiment, tests of the effect of artificially induced changes on the susceptibility of monkeys to intranasal instillations of virus were carried out on a series of 90 castrated immature monkeys, 45 of which received a course of injections of estrogen (stilbestrol). The disease developed in 34 of the 45 castrated animals and in 21 of the 45 castrated animals treated with estrogen; in the latter group in which the disease developed its appearance was four days later than in the control animals. These results indicate not only that the estrogen enhanced the resistance to the infection but that the interval from the first instillation of the virus to the onset of the disease was comparatively longer. The second series of experiments consisted of comparative assays of urinary estrogen on patients with poliomyelitis and on control persons of the same ages. The results indicate a higher average excretion of estrogenic substance in the group of patients with poliomyelitis. Palmer, Philadelphia.

Progressive Facial Hemiatrophy. M. O. Wolfe and M. L. Weber, J. Nerv. & Ment. Dis. **91**:595 (May) 1940.

Wolfe and Weber describe the case of a man aged 39 who, having previously suffered from hypohidrosis and gynandromorphism (absence of beard, soft hair, rounded body contour, prominent breasts and female escutcheon), began at the age of 21 to exhibit progressive atrophy of the left side of the face. Infrequent attacks of unconsciousness without convulsions began to occur a few years later. There were depression of the left temple, atrophy of periorbital fat with apparent enophthalmos and a widened palpebral fissure on the left, and a shrunken, cicatricial appearance of the left side of the chin. Alopecia above the left side of the forehead and scantiness of the left eyebrow were noted. The tip of the nose was drawn slightly to the left, and the soft palate was grooved on the left side. The tongue was symmetric. Roentgen studies revealed bony atrophy and increased radiolucency of the left side of the skull. Injection of pilocarpine produced profuse sweating on the right side of the face and but slight moisture on the left. Photographs taken at the ages of 31 and 39 revealed definite progression of the atrophy. The authors attribute the condition to a disturbance of the sympathetic nervous system.

Mackay, Chicago.

Fatal Chronic Dermatomyositis with Scleroderma. Radermecker, J. belge de neurol. et de psychiat. **40**:83 (Feb.) 1940.

Radermecker reports a case of chronic dermatomyositis with scleroderma, terminating fatally, in a man aged 45. The primary symptoms were extreme fatigue, loss of weight and atrophy of the muscles of the shoulder girdle, neck and trunk. Later there were inability to open the mouth and atrophy in the region of the temporal fossae. The skin was pigmented, atrophic, wrinkled, hard and dry. Biopsy of the deltoid muscle revealed intense, diffuse lymphocytic infiltration with replacement of muscle fibers by interstitial tissue, and examination of the skin showed atrophy with almost complete absence of papillae.

De Jong, Ann Arbor, Mich.

Physiological Significance and Morphology of the Carmine Cell in the Cat's Anterior Pituitary. H. B. Friedgood and A. B. Dawson, Endocrinology **26**:1022 (June) 1940.

In a series of three previous articles, Friedgood and Dawson have reported striking changes in the composition of the acidophilic cells of the anterior lobe of the pituitary of the female rabbit after mating. This reaction was demonstrated

by means of a method which separated the acidophilic cells into two distinct groups, the ordinary, or standard, acidophil taking on a yellow color with orange, while the other acidophilic cells, which became conspicuous during sexual activity, acquired a brilliant red stain as a result of their special affinity for azocarmine and were characterized by the coarseness and refractivity of their granules.

The present article reports the results of the extension of this study to the cat, which, because of its relatively long, well defined anestrous period and a characteristic spontaneous behavior pattern during estrus, is a more suitable subject than the rabbit, the inconstancies of which with regard to the sexual cycle make it difficult to ascertain exactly the degree of sexual excitement.

Twelve cats were studied by histologic examination of the pituitaries during the first twenty-four hours after mating and/or stimulation of the cervix uteri with a glass rod and these results correlated with sexual behavior before, during and after mating and the condition of the ovarian follicles and ova as observed at autopsy. Comparison was made with similar histologic studies on groups of anestrous and preestrous cats. The carmine cells were found to be absent in anestrous, sparsely present in preestrous and markedly increased in number during estrus. A definite characteristic change in the pattern of distribution and a progressive increase in the number of carmine cells after mating were noted in every animal, the carmine cells reaching a maximum within five to six hours and practically disappearing at the end of fourteen hours.

This temporal sequence of events in the pituitary gland was found to parallel closely the cytologic changes which occurred in the mature ovarian follicle and also to follow closely the sexual behavior of the animal. It is therefore concluded that the function of the carmine cell is directly concerned with gonadotropic activity which is rapidly initiated in the pituitary gland by the sex act. Certain theoretic considerations suggest that it is most closely concerned with the secretion of luteinizing hormone.

PALMER, Philadelphia.

INSULIN LIPODYSTROPHY IN DIABETIC CHILDREN. M. L. SALDÚN DE RODRÍGUEZ, Arch. de pédiat. d. Uruguay **11**:642 (Aug.) 1940.

Saldún de Rodríguez reports 3 instances of lipodystrophy in children occurring in the course of the second or the third year of insulin therapy. This incidence occurred in a group of 38 children with diabetes living under fairly satisfactory conditions of proper diet and insulin therapy. The insulin was administered in two or three daily doses of from 2 to 7 units for each injection, or in a daily total dose of 4 or 5 units. The injections were given in the external aspect of either thigh. The lipodystrophic lesions were symmetric and located at the seat of injections in 2 cases and in the gluteal region in the third case. The author believes that insulin lipodystrophy, produced either locally or at a distance, is due to repeated injections of insulin in the same area in children predisposed to this condition from a disturbance of the nervous system. Injections of insulin make the region less sensitive to pain. For this reason the patient and the family ask the physician to give the injections in the same area. This practice must be avoided in order to prevent the occurrence of lipodystrophy.

J. A. M. A.

Treatment, Neurosurgery

THE TREATMENT OF ALCOHOLISM BY ESTABLISHING A CONDITIONED REFLEX. WALTER L. VOEGTLIN, Am. J. M. Sc. **199**:802 (June) 1940.

Voegtlin applied the principle of conditioned reflex to the treatment of alcoholism in which the action of certain nauseant drugs is utilized to elicit the unconditioned reflex of nausea and vomiting. The sight, smell and taste of alcoholic beverages serve as the conditioned stimulus, and thus a conditioned reflex can be established. The establishment of a conditioned reflex aversion to alcohol is undertaken during five to seven séances or treatments, with periods of rest between. The average stay in the hospital is five days. The author's choice of nauseant

was emetin and apomorphine hydrochloride. He found aversion to the sight and smell of liquor to be very marked after completion of the course of treatment. The following routine is used: The patient is made comfortable in a treatment room, and the appropriate dose (6 to 12 minims [0.372 to 0.744 cc.]) of the emetine-pilocarpine-ephedrine mixture is given hypodermically. The first offering of liquor should be given within several seconds before the onset of nausea, and certainly under no condition should it be withheld until either nausea or salivation has occurred. After the onset of nausea, all types of liquor are forced on the patient, it being made certain that each empty glass is smelled deeply. A total of 685 patients with chronic alcoholism were treated by this method. The exact status of 538 of these patients was known. The percentage of sobriety was remarkably constant, varying only between 62 and 69 per cent. The author believes that with this method one can conservatively expect 64.3 per cent of total and permanent cures. By cure is meant total and permanent abstinence from alcohol of all types. The average age of admission was 41.5 years. Delirium tremens developed in only 14 (2 per cent) of the total number of treated patients. Failures are attributed in very few instances to the inability to establish a satisfactory conditioned reflex. Relapses occurring before the sixth month are almost without exception characterized by gross psychopathic traits. Younger persons and women are less promising patients from the standpoint of ultimate cure than are mature men.

MICHAELS, Boston.

ADVANCES IN TREATMENT OF DEMENTIA PARALYTICA BY COMBINED ARTIFICIAL FEVER AND CHEMOTHERAPY. A. E. BENNETT, J. C. NIELSEN and A. H. FECHNER, Nebraska M. J. **25**:1 (Jan.) 1940.

In comparing the clinical rates of remission of dementia paralytica following the various types of treatment, Bennett and his colleagues find that 12 per cent of patients obtained clinical remissions from chemotherapy (tryparsamide) alone, 42 per cent from malarial fever followed by chemotherapy and 53 per cent from combined artificial fever and chemotherapy. Of 20 patients with early dementia paralytica, a full remission was obtained in 65 per cent and partial improvement in 30 per cent. Complete serologic reversal of the spinal fluid was obtained in 40 per cent, with partial reversal in 30 per cent, after combined artificial fever and chemotherapy. Of 10 patients suffering from dementia paralytica with tabes a full remission was obtained in 50 per cent and a partial remission in 30 per cent. The serologic reactions of the spinal fluid were reversed completely in 40 per cent and partially in 10 per cent. Of 28 patients with advanced dementia paralytica committed to a state hospital, 54 per cent obtained a full clinical remission and 28 per cent a partial remission. A complete serologic reversal of the spinal fluid occurred in 28 per cent and a partial reversal in 50 per cent. Of 12 patients failing to obtain a full remission from malarial inoculation, 33.3 per cent obtained a full remission and an additional 25 per cent were improved after fever and chemotherapy. The serologic reactions of the spinal fluid were reversed to negative in 33 per cent and improved in 41 per cent. The results from artificial fever, fifty hours at a temperature above 105 F., combined with mapharsen for the entire group of 70 patients representing all stages of dementia paralytica were full remissions in 53 per cent and improvement in an additional 28 per cent. A complete serologic reversal of the spinal fluid occurred in 34 per cent, with partial reversal in an additional 37 per cent.

J. A. M. A.

AMBULATORY INSULIN TREATMENT OF MENTAL DISORDERS. F. POLATIN, H. SPOTNITZ and B. WIESEL, New York State J. Med. **40**:843 (June 1) 1940.

Polatin and his associates gave small doses of insulin hypodermically to 22 unselected patients with mental disease of functional or organic type. The functional group included 18 patients with schizophrenia, manic-depressive psychosis or psychoneurosis. The organic group consisted of 4 patients with definite cerebral

lesions associated with hypertensive cardiovascular disease, cerebral arteriosclerosis, an organic syndrome following removal of a pineal tumor or organic disease of the brain of an undetermined type. Patients were given one hypodermic injection of insulin daily at 5 a. m. and had the usual hospital breakfast at 8 o'clock. The initial dose was 5 units. This was increased daily by 5 units until a mild hypoglycemic shock, characterized by the usual symptoms of weakness, giddiness, tachycardia, vasomotor alterations, excessive perspiration and some drowsiness, was obtained. Usually the hypoglycemic symptoms began about two hours after the injection and gradually increased in severity. Hypoglycemia was permitted for from fifteen to forty-five minutes. The 40 units of insulin in one dose was sufficient to produce the desired effect. The hypoglycemic state was usually terminated with breakfast. During hypoglycemia the patients were up and about. The mild hypoglycemic symptoms did not prevent the patients from feeding themselves at breakfast without any assistance. The 22 patients were treated over a period ranging from one week to eighteen months. Transitory alterations in the mental status of the patients were observed during the daily treatment period and in some instances continued for a few hours thereafter. Agitated and excited patients were quieted, states of confusion were cleared and dulness and apathy gave way to increased alertness. Such beneficial changes gradually persisted for longer periods after each treatment until definite clinical improvement was maintained. Even the 4 unimproved patients were influenced by the insulin treatment so that nursing and feeding problems were simplified. All patients gained weight, with an accompanying increase in appetite. One patient recovered, 12 were much improved and 5 were slightly improved. The much improved patients were able, despite residual symptoms, to adjust themselves socially at a level paralleling their premorbid behavior. The slightly improved patients showed definite increased ability to adjust themselves to the hospital routine but did not reach their premorbid behavior level because of residual symptoms. No coma, allergic manifestations, convulsions or observable injuries occurred during treatment.

J. A. M. A.

COMPARISON OF BELLABULGARA AND OTHER FORMS OF MEDICATION IN TREATMENT OF CHRONIC ENCEPHALITIS. J. B. NEAL and S. M. DILLENBERG, New York State J. Med. **40**:1300 (Sept. 1) 1940.

According to Neal and Dillenberg, the Matheson Commission for encephalitis research began about two years ago the use of white wine decoction of Bulgarian belladonna in treating patients with chronic encephalitis. When it was found that this decoction deteriorated on standing, a tablet was prepared to insure a stable preparation. Approximately 100 patients have been treated with these preparations and with the tablets. Practically all of these patients had previously tried other forms of symptomatic treatment, such as scopolamine, stramonium, amphetamine sulfate or combinations of these medicaments. The results with the Bulgarian belladonna were far superior to those obtained with any other form of symptomatic treatment. About one third of the patients can be considered greatly improved, one half moderately improved and the remainder slightly improved. Many of the patients have been under treatment for at least a year and a half, and the improvement has been maintained. In certain cases the improvement is increasing. It was possible to make a comparative study of 23 patients treated with tablets of Bulgarian belladonna and 21 treated with a synthetic preparation containing about 0.5 mg. of akaloids in the following combination: hyoscyamines 0.45 mg., atropine 0.037 mg. and scopolamine hydrobromide 0.012 mg. All the patients were in a far advanced stage of chronic encephalitis, and all had previously received various forms of medication. The severity of encephalitis was as nearly equal as possible in the two groups. The results obtained with the tablets of Bulgarian belladonna were far superior to those with the synthetic preparation. All except 3 of the patients receiving the tablets showed subjective improvement. They felt stronger, slept better, had less feeling of tension and were more cheerful and cooperative.

Objectively, there were better facial expression, less spasticity and tremor, greater facility in motion and improvement in speech. Increased salivation was entirely relieved in practically all cases. The improvement of the patients treated with the synthetic preparation was similar but not so marked. The synthetic preparation produced more frequent and severe toxic effects, and with smaller doses, than did the Bulgarian belladonna. It is interesting that when the comparative study was ended and the patients were returned to the previous medication, almost all of those treated with tablets of Bulgarian belladonna requested that these tablets be continued, whereas the patients who had received the synthetic preparation for the most part accepted the return to the former medication without comment. The authors conclude that Bulgarian belladonna is the most beneficial drug available in the treatment of chronic encephalitis.

J. A. M. A.

Operation for Relief of Epilepsy Following Certain Traumatic and Inflammatory Lesions of Brain. J. M. Meredith, South. Surgeon **9**: 86 (Feb.) 1940.

Meredith devised an operation for the relief of epilepsy following cerebral trauma with resulting obliteration of the basilar cisterns. The requirements for success are (1) the presence of definite internal (communicating) hydrocephalus (as demonstrated encephalographically) with (2) little or no air in the subarachnoid spaces overlying the cerebral hemispheres or in the basilar cisterns. The operation consists of a transcortical incision and formation of a large stoma into the lateral ventricle through a relatively unimportant portion of the less dominant cerebral hemisphere, together with excision of the choroid plexus in that ventricle; this results in a short circuit of the fluid around the obstructed basilar cisterns and a reduction in the total amount of fluid formed. Convulsions have not recurred up to twenty-three months after operation in the author's case, although phenobarbital and other anticonvulsive drugs were discontinued one year after operation. Before the surgical operation the patient was having several severe convulsions every month, in spite of dehydration and phenobarbital therapy. The author states that an encephalographic picture, like that in his case, is occasionally seen in cases of epilepsy occurring either after trauma or after an inflammatory lesion of the brain. He urges that further use be made of the operative procedure described in an effort to combat the devastating effects of convulsive disorders.

J. A. M. A.

A Review of Cases of Injury to the Vertebrae Occurring in the Royal Air Force. P. A. Hall and G. H. Morley, Brit. M. J. **1**:159 (Feb. 3) 1940.

Hall and Morley analyze 57 cases of injury to the vertebrae occurring in the last five years in the Royal Air Force, 9 of which were the result of flying accidents and the rest of other accidents. The method of treatment generally followed in these cases was that of Watson Jones and Bohler, that is, early reduction by hyperextension and fixation in plaster of paris. The authors favor early ambulation. Open operation was performed once in the series, in a case of cervical dislocation, and laminectomy was not done in any instance. The authors describe a case of bilateral cervical dislocation which was not reduced by traction until a pull of 160 pounds (72.6 Kg.) was applied.

From the current literature it was found that there is general agreement that crush fracture of the body of a vertebra should be treated by early reduction through hyperextension and adequate fixation. In cases in which the complication of paralysis exists, reduction should be carried out early. Most authorities agree that laminectomy is rarely indicated. Skeletal and postural traction have been suggested in the reduction of cervical dislocations, but the authors favor personally controlled traction during fluoroscopy.

Echols, New Orleans.

CONVULSION THERAPY OF PSYCHOSES. A. M. WYLLIE, J. Ment. Sc. **86**:248 (March) 1940.

Wyllie reports on the results of convulsion therapy in 144 cases of various psychoses. The term "recovered" was used to indicate that all symptoms have disappeared, that some degree of insight has been restored and that the patient is fit to be discharged to home conditions and to take up his former activities. The term "improved" indicated that a great change for the better has occurred in the patient's behavior and habits but that symptoms may remain and that insight has not been restored completely. Some of these patients are fit to be discharged from hospital care. Of 14 patients, in whom schizophrenia had existed for less than one year, 7 recovered and 6 were improved, while only 3 of 68 patients having the disorder for more than one year recovered. Although the number of cases of the early stage in his series is small, the author is convinced that convulsion therapy is of definite value in the early treatment of schizophrenia. This is in harmony with the observations of most workers. Thirty-three of the 68 patients were greatly improved. Of 9 patients with paraphrenia of more than one year's duration, none recovered but 4 improved. The results are similar to those in the group with chronic schizophrenia. Patients in both the melancholic and the manic phase of manic-depressive psychosis responded immediately to the treatment. Of 27 such patients treated, 17 recovered and only 1 was not improved. A happy feature was the rapid disappearance of suicidal tendencies. Of 11 patients with involutional melancholia who were ill less than two years prior to treatment, 7 recovered. A considerable number of patients with involutional melancholia that would not recover spontaneously but would drift into chronicity could be saved by convulsion therapy. The average duration of illness of the patients who recovered (including 1 who was ill five years) was one year and two months, while the average duration of illness prior to treatment in the group who did not recover was five years and two months. In all, 24 patients were treated; of these, 8 recovered, 8 were improved and 8 were unimproved. The rate of recovery from manic-depressive and involutional melancholias is not comparable with the spontaneous rate of recovery. Only patients who did not show signs of recovery after a reasonable period were submitted to convulsive treatment. There were only 2 patients with psychoneurosis. The first, with obsessional neurosis, was greatly improved, and the second, with hysteria, recovered. For involutional melancholia and the manic-depressive psychosis usually from two to seven convulsions were required to cut short the illness, while schizophrenic patients required a longer course. Relapses are common. The problem of how long to continue inducing convulsions, and the success of the treatment, rest on the physician's clinical intuition. If too few convulsions are induced, relapse is likely to follow, while continuance of the treatment after the maximal improvement has been attained subjects the patient to unnecessary risk and may be harmful.

J. A. M. A.

FRACTURES OF THE NECK OF THE FEMUR IN CONVULSIVE THERAPY. W. GISSANE, D. BLAIR and B. K. RANK, Lancet **1**:450, 1940.

Carp, in 1939, said that metrazol produces "the most intense form of muscular contractions to which the human frame is ever subjected." As a result, major fractures are not uncommon with metrazol-induced convulsions, but are comparatively rare in epileptic fits. Four cases of fracture of the neck of the femur are reported in a group of 96 patients subjected to metrazol or triazol convulsions. All 4 were intracapsular, and in 2 cases the fractures were bilateral. Other injuries in the same group were: 2 compression fractures of the vertebral bodies and several dislocations of the temporomandibular joint. The 4 patients were from 35 to 41 years of age. Fractures occurred at the sixth, fifth, seventh and first convulsion, respectively. Three were treated with Smith-Petersen nails and made good recoveries. The fourth, after traction had failed, was subjected to

bilateral subtrochanteric osteotomy and died after the operation. Convulsion therapy should not be used with elderly patients. A minimal number of injections should be made. The skeletal system should be examined routinely. The fractures are treated by the usual methods, preferably with a Smith-Petersen nail.

NORCROSS, San Francisco.

Cerebellum and Brain Stem

RHYTHMIC AND SYNCHRONOUS MYOCLONIAS OF THE PHARYNX AND LARYNX. A. KREINDLER, Schweiz. Arch. f. Neurol. u. Psychiat. **43**:79, 1939.

Rhythmic myoclonus of the palate and pharynx in the great majority of previously reported cases has been due to vascular accidents. For this reason, most of the patients have been older persons. The condition has been attributed to a lesion of the central tegmental tract with pseudohypertrophic degeneration of the corresponding inferior olive. In cases in which the central tegmental tract was not involved a lesion of one of the dentate nuclei has been associated with pseudohypertrophic degeneration of the contralateral inferior olive. The most striking clinical features are the constancy of rhythm and the fact that all the muscles participating in the myoclonic movements contract synchronously.

A woman aged 63 suffering with hypertension had quickly recovered from right hemiplegia three years previously. Symptoms of pseudobulbar palsy had developed after a second vascular accident, with left hemiplegia, six months before. Whenever the patient looked to the right rhythmic movements of the eyeballs were observed. These movements were not on the order of nystagmus, as the slow and quick components characteristic of the latter condition were lacking. Synchronous with the movements of the eyeballs were other myorhythmias in the lower half of the face on the right side, the right sternocleidomastoid muscle, both sides of the soft palate and the posterior wall of the pharynx. Muscles of the floor of the mouth, i. e., the digastric and mylohyoid muscles, were likewise involved, and up and down movements of the thyroid cartilage were noted. Of the intrinsic musculature of the larynx, only the arytenoid muscles showed myoclonic movements.

Graphic records of the myoclonic movements of the right side of the face and the right sternocleidomastoid muscle were obtained with the use of Marey tambours. Movements of the palate were recorded by means of a small balloon placed within the patient's mouth and connected with a tambour. Muscles studied in this manner were found to contract with a synchronous rhythm varying from 85 to 110 contractions per minute. The individual movements consisted of a quick contraction and a slower relaxation which was followed, after a short pause, by a slower contraction in the opposite direction. The movements did not cease during the act of swallowing; their amplitude was greater during inspiration than during expiration and their frequency could be increased by pressure over the carotid sinus.

Persistence of the myoclonic movements during the act of swallowing is believed to indicate that rhythmic impulses responsible for them are conducted to the bulbar nuclei from higher centers, but not by way of the pyramidal tracts. Significance is attached to the fact that the sucking movements of nurslings have a rhythm of 80 to 90 per minute, which approaches closely the rhythm of the myoclonic movements which have been described. Both types of movement, furthermore, involve similar groups of muscles. Kreindler and his associates have shown that the excitability of vestibular centers can be altered by pressure over the carotid sinus. It would appear, therefore, that stimulation of the carotid sinus has an influence on several, perhaps all, of the bulbar centers.

The medulla oblongata is the seat of certain automatisms essential for life, i. e., circulation of the blood and respiration. It seems likely that centers for the control of the musculature of the pharynx, larynx, face and eyes have a similar capacity for automatic and rhythmic activity, but under normal conditions are

inhibited in this respect. The view is expressed that a lesion either of a supranuclear center or of a tract leading to the centers for control of these muscles releases this automatic activity and thus produces the myoclonic movements.

Automatic activity, which has the characteristics of rhythmicity and periodicity, is a property of centers scattered throughout the central nervous system. It is not necessarily induced by afferent impulses. Most ganglion cells, in fact, have a rhythmic activity peculiar to themselves, the synchronized activity of great cell masses being well illustrated by electroencephalographic tracings. Kreindler and his co-workers have observed rhythmic movements of the tail in decerebrated cats. Action currents obtained from the isolated medulla oblongata of fishes show a rhythm similar to that of respiration. The respiratory center functions automatically under normal conditions, while other centers betray their capacity for automatic activity only when released from the control of higher levels.

DANIELS, Denver.

Diseases of Skull and Vertebrae

FRONTAL BONE OSTEOMYELITIS. A. C. JONES, Ann. Otol., Rhin. & Laryng. **49**:713 (Sept.) 1940.

Jones reports 13 cases of osteomyelitis of the frontal bone and emphasizes the necessity for early diagnosis. He stresses the fact that swelling, edema and pain over the frontal sinus are of more value than a roentgenogram, as the infection is existent from seven to ten days before there can be roentgenographic evidence of it. In 2 of the author's cases the condition followed injury and was not connected with sinal infection; in 4 there was intracranial involvement, and in 7 there was no such involvement. He does not think that any definite operative procedure can be followed in these cases. It is not necessary to block off and remove a whole area of the frontal bone because the diploic spaces are tortuous. The operative procedure which he uses follows the diploic spaces. The incision should be sufficiently large to uncover a large amount of bone for inspection, and removal of bone should extend laterally far enough to reach the outer limit of the frontal sinuses. He has secured good results by more conservative incisions than that from eyebrow to eyebrow and splitting up the middle of the forehead. He has used the hairline incision as brought out by Furstenberg with almost no visible scarring, being careful to preserve the periosteum. With plenty of assistance in elevating the scalp, an excellent view can be obtained of the questionable area. This incision also leaves little scarring. The end results in his cases indicate that the enormous disfiguration caused by keeping the flaps separated during the healing is not necessary. He concludes from a rather incomplete survey of the literature and his observations that generalized osteomyelitis if often inexcusably overlooked.

J. A. M. A.

COMPRESSION OF SPINAL CORD AND NERVE ROOTS BY HERNIATION OF THE NUCLEUS PULPOSUS IN THE CERVICAL REGION. BYRON STOOKEY, Arch. Surg. **40**:417 (March) 1940.

In 1927 Stookey reported for the first time a group of unusual "tumors" arising from the cervical intervertebral disks. In view of present knowledge the then called ventral extradural cervical chondroma is now believed to be not a neoplasm but rather a portion of the nucleus pulposus protruding through the annulus fibrosus into the vertebral canal. A history of sudden onset of symptoms associated with injury is rarely obtained in cases of herniation of the cervical region because of the relative mobility of the vertebrae in this region. The majority of herniations of cervical disks occur in men of late middle age as a result of repeated minor strain and stress. The average age in this series was 53.

Three groups of symptoms can be connected with this lesion in the cervical region, depending on the size and position of the protruded portion. When the

ventral pressure is bilateral, the initial symptoms are pain and a sensation of intense cold, with numbness, spasticity and weakness in both lower extremities and gradual weakness and hypotonia in the muscles of the upper extremity together with atrophy and fibrillation, although the latter may be absent. The sensory disturbances are bilateral, involving pain and temperature sensation, with blunting of tactile discrimination as well as crude tactile sensation. Vibratory sense may also be impaired, although muscle, joint and tendon sense may or may not be affected.

If, however, the protrusion is narrow and situated in the midline, pressure may be exerted only on the ventral gray column and on both emerging ventral roots, without impingement on the more laterally placed spinothalamic tracts or the more dorsal pyramidal tracts. In this event the signs are referable to the ventral gray columns alone—atrophy, hypotonia and fibrillary twitchings limited to the muscles supplied by a single segment. Recently, an exploration was done on a patient with these signs, due to a protruded disk of this type. No sensory changes were observed, and no signs of disturbance of the long fiber tracts were elicited. A definite ventral protrusion compressing both ventral gray columns and both ventral roots at their emergence was encountered.

When the protruded disk lies laterally and thus compresses the ventral columns of the cord, signs of involvement of the unilateral pyramidal tract in the lower extremity on the side of the protrusion are produced, with local weakness and atrophy on the same side in the muscles of the cervical segments at the level of the compression. Changes in pain and temperature sense occur on the opposite side of the body at a level several segments lower than the focal motor signs. Thus the syndrome consists of focal atrophy of the lower motor neuron type at the level of the lesion, spasticity and pyramidal tract signs of the upper motor neuron type below the level of the lesion on the same side and dissociated sensory changes on the opposite side. The presenting symptom in these cases may be pain or stiffness of the neck, associated with pain or weakness in the region of the shoulder girdle, arm, forearm or hand, depending on the segment involved. The motor signs produced by pressure on the ventral matter consist, as suggested, in rather sharply localized atrophy and fibrillations involving the muscles on the same side and indicating clearly the level of compression of the cord. Thus, with pressure at the level of the fifth and sixth cervical segments the deltoid, biceps, supraspinatus and supinator longus muscles are affected, whereas pressure at the level of the eighth cervical segment produces fibrillation and atrophy of the intrinsic muscles of the hand. The sensory disturbances, loss of pain and temperature sensations on the opposite side, are due to pressure on the spinothalamic tract. While the sensory changes are definite, they are likely to be misleading as an indication of the site of compression, since the sensory level is several segments lower than the motor level. This is to be explained by the fact that the incoming pain and temperature fibers cross obliquely in the spinal cord and do not reach the contralateral spinothalamic tract for a distance of several segments. A slight blunting of crude tactile sensation may occur, probably due also to pressure on the spinothalamic tract. Tactile localization, muscle-joint sense and vibratory sensation, all carried in the posterior columns of the cord, are unaffected. Because of the atrophy and dissociated sensory changes, this syndrome is frequently attributed to intrinsic disease of the cord. In the third group of cases the herniated nucleus is situated somewhat more laterally than in the other groups, compression being exerted not on the ventral column of the cord but on a nerve root near its emergence from the dura, with production of symptoms and signs referable to the root affected. Focal muscle atrophy and hypotonia limited to the distribution of the roots involved are found. The sensory signs are purely subjective, such as burning, gnawing and tingling sensations, which may be increased by movement of the extremity. Root pain and focal motor signs are the only diagnostic features. Lesions of this group are rare.

Evidence of spinal fluid block is rare in cases of herniation in the cervical region. Iodized poppyseed oil should not be used in these cases, for the necessary manipulations would almost certainly result in the oil reaching the cranial cavity. Air myelography is useless. Roentgen examination may show a significant narrowing of an intervertebral space, which is important when the narrowing occurs at the level shown by clinical symptoms to be involved. The best surgical procedure is hemilaminectomy. The operative results are not as satisfactory as those which may follow removal of a lumbar disk. In part, at least, this is due to difficulties in diagnosis resulting in long-continued pressure on the cord and consequent serious degeneration of fiber tracts. GRANT, Philadelphia.

CLINICAL ASPECTS OF PROTRUDED INTERVERTEBRAL DISK. HARRY B. MACEY, Arch. Surg. **40**:433 (March) 1940.

The clinical history resulting from a posterior protrusion with accompanying neural irritation commonly follows one of two patterns: 1. There may be recurrent "low backache" with the initial onset attributed to an injury severe enough to be remembered. There also may be an association of repeated injuries with an acute onset of sciatic pain following an apparently trivial injury, such as slipping, tripping or falling in a sitting position, in which there occur sudden flexion and torsion of the spinal column. The sciatic pain may be continuous or recurrent. There may be an associated paresthesia, which is commonly complained of in the form of numbness, tingling or needle-like pains over the buttocks, the posterior aspect of the thigh, the posterolateral aspect of the leg or the dorsum of the foot. 2. There may be backache and sciatica together, continuous and with or without a history of remembered injury. The injury is frequently trivial and seemingly insufficient to cause an acute rupture of the annulus fibrosus. In this type paresthesia is also a common complaint. In the presence of persistent sacral pain without disturbance of the achilles tendon reflex, posteriorly protruded disk at a high level should be suspected.

The sciatic pain is aggravated by activity, coughing, sneezing and motions which induce traction on the nerve roots. On close questioning regarding relief with rest, it is found that most of the patients become free from pain by lying absolutely immobile and that any motion produces the pain. Many positions may be assumed, the most common of which is lying on the side with the spinal column and thighs flexed. From this clinical picture there may be many variations, such as relief on walking or standing, and pain only in the buttock, thigh or leg. There are varied levels of pain and anesthesia. The effect of traction on the extremities varies; in some cases the sciatic pain is intensified and traction is intolerable, while in others traction gives temporary relief, the pain recurring when activity is allowed. There are other cases in which traction affords periods of complete relief.

From the foregoing data it is readily seen how difficult it is to draw any definite conclusion other than that the syndrome may include the following manifestations: (1) recurrent backache and recurrent sciatic pain, (2) continuous backache and recurrent sciatic pain, (3) continuous backache and continuous sciatic pain, (4) continuous sciatic pain without backache or (5) recurrent sciatic pain without backache.

In 50 of the group of 100 cases there was unilaterally limited "straight leg raising"; in 24 there was bilaterally limited "straight leg raising," and in 26 the patients were considered normal in this respect. In 17 cases there was atrophy of either the buttock or the extremity or both.

The characteristic position of the spinal column in the cases of acute involvement was a list to the unaffected side, with scoliosis of the lumbar vertebrae. This was noted in 33 of 100 cases. In only 5 cases was there a list to the affected side. In 24 cases the posture was good; in 21 cases no mention of posture was made, and one assumes that it was good. In 1 case there was alter-

nating scoliosis, which is almost pathognomonic of a bilateral or midline posterior protrusion; however, there is commonly a bilateral protrusion without alternating scoliosis. In 16 cases there was obliteration of the lumbar lordosis with generalized flattening of the back.

In 50 cases tenderness was elicited over the lumbosacral joint and was felt to arise from pathologic changes in this joint. Possibly in some cases the tenderness resulted from a lesion of the interspace between the fourth and fifth lumbar vertebrae. In 50 cases tenderness could not be elicited on physical examination or was of such little significance that it was not noted. In 39 cases there was tenderness over the region of the sacroiliac joint on the affected side, which is probably of little clinical significance. In 80 cases, or 80 per cent, there was definite limitation of motion, particularly in flexion of the spinal column.

Of 98 cases in which fluoroscopic examination with radiopaque oil was done, there were 93 in which a positive defect was found, 4 in which the procedure was a failure and 1 in which a protruded disk was found at the interspace between the fourth and fifth lumbar vertebrae at operation after the results of roentgen examination had been reported as negative. In the 2 remaining cases of the series direct exploration was carried out without roentgen examination.

In 34 patients changes were noted on roentgen examination of the bony structures in association with the posterior protrusion; there were 1 with spondylolisthesis, 2 with "facet changes," 3 with hypertrophic changes and 28 with narrowing of the lumbosacral or of the interspace between the fourth and fifth lumbar vertebrae, all corresponding to the site at which the posterior protrusion occurred. Of this group of 28 patients, 13 had had from many months to years of backache.

Forty-one of the posterior protrusions occurred at the fourth and fifth lumbar interspace, 46 at the lumbosacral joint, 8 at the third and fourth lumbar interspace and 1 at the second and third lumbar interspace. Four patients showed multiple protrusions. Of this group there were 28 midline or bilateral protrusions of the disks. Each of the remaining 72 protrusions was unilateral.

The most important finding in neurologic examination was a diminished achilles tendon reflex; however, a normal reflex does not preclude the finding of a posteriorly protruded disk. In 66 of the group of 100 cases there was evidence of a diminished achilles tendon reflex. Of the group of 100 cases, there were 12 in which there was bilateral sciatic pain and in which a bilateral protrusion was found. In 96 cases the average protein content of the spinal fluid was 53.8 mg. per hundred cubic centimeters. In 36 cases the protein content did not exceed 40 mg. per hundred cubic centimeters. In 4 cases it was 45 mg. In the remaining 56 cases the protein content per hundred cubic centimeters of spinal fluid was more than 45 mg., and was considered to be of definite pathologic significance. The highest protein content for any individual patient was 220 mg. per hundred cubic centimeters of spinal fluid.

A test is mentioned which is thought to be of significance in examination of patients with posterior protrusion. This consists of sudden unexpected hyperextension of the lower lumbar vertebrae. When the result is positive, pain is reproduced over the course of the affected sciatic nerve. The mechanism whereby this occurs is probably a narrowing of the posterior interspace with a sudden relative increase in the posterior bulge, resulting in sudden pressure on the nerve root.

GRANT, Philadelphia.

Society Transactions

NEW YORK NEUROLOGICAL SOCIETY

LEON H. CORNWALL, M.D.

President, in the Chair

Regular Meeting, Oct. 1, 1940

Presidential Address: Some Contrasts Between Medical Science and Political Philosophy. DR. LEON H. CORNWALL.

The Wernicke Syndrome. DR. NORMAN JOLLIFFE (by invitation), DR. HERMAN WORTIS and DR. HARRY D. FEIN (by invitation).

Twenty-seven cases of Wernicke's syndrome (3 occurring in nonalcoholic persons) are analyzed and the following conclusions reached:

1. The syndrome as originally described by Wernicke is probably a combination of several nutritional deficiencies affecting the nervous system and need not be complete in any case. It is of course possible that the exact syndrome which Alexander has produced experimentally in pigeons may on occasions occur in uncomplicated fashion in man, but except for ophthalmoplegia the symptoms would be difficult to evaluate.

2. Our results indicate (*a*) that the ophthalmoplegia is a vitamin B_1 deficiency and (*b*) that the clouding of consciousness may be related to anything which interferes with proper metabolism of the brain. Among the known offenders are lack of carbohydrate, lack of oxygen, lack of vitamin B_1, nicotinic acid and riboflavin and probably lack of many other substances now under investigation.

3. The ataxia is difficult to evaluate, and its response to therapy has not yet been worked out.

4. Other deficiency syndromes may and do superimpose themselves on the more usual Wernicke picture, and these require specific treatment.

5. The ophthalmoplegia is invariably preceded or accompanied by peripheral neuropathy. This tends to confirm Alexander's thesis that smaller amounts of vitamin B_1 are needed to prevent the polioencephalopathic changes than are necessary for antineuritic action.

6. Delirium, with its marked increase in psychomotor activity and hence in total metabolism, frequently precedes the development of this syndrome.

7. In the recovered patients the development of a Korsakoff syndrome is the rule. This does not show a consistent response to vitamin B_1 therapy, as has frequently been claimed.

8. The inclusion of all "alcoholic" encephalopathic states under one term, such as alcoholic encephalopathy, is not justified. We believe that the clinical syndrome or syndromes presented by each patient should be labeled, the response of each syndrome to specific therapeutic agents recorded and, finally, the metabolic and pathologic changes found in each subject correlated with the clinical syndromes observed during life. If this is done, one will eventually be able to classify each of the syndromes from an etiologic, metabolic and pathologic point of view. Furthermore, the administration of the specific therapeutic agent should result in prompt recovery, unless irreversible changes have already set in.

DISCUSSION

DR. HENRY ALSOP RILEY: The condition, first described by Wernicke in 1881, has always been looked on as essentially a generalized disturbance, showing evidence of widespread involvement of the nervous system with focal concentration of effects in the upper part of the brain stem. From the beginning it has been considered due to some form of intoxication, but recently the possibility of a nutritional or dietary cause has taken the center of the stage.

In the first case of a nonalcoholic patient reported by Wernicke evidence appeared involving the gastrointestinal tract and the absorption of food material; this is of great interest as extensive gastrointestinal symptoms and signs have been recorded in subsequent series of cases. Disorders of the gastrointestinal tract have figured prominently in the history and examination of patients with this disease. Malignant disease and the chronic changes in mucous membranes so frequently the result of the overuse of alcohol have been repeatedly demonstrated.

The vitamin factor, first mentioned, according to the authors, less than ten years ago, has received increasing attention, both clinically and experimentally, Alexander's suggestion being that vitamin B_1 possesses an antiangiodegenerative function in addition to its many other characteristics. The demonstration that hemorrhagic superior polioencephalitis cannot be induced under conditions which will regularly produce it if adequate thiamine hydrochloride is administered presents a fact that is difficult to interpret in any way other than that this vitamin is vitally involved in the picture.

That the disease has appeared in many cases in which alcoholism was not present proves that alcohol is not a primary factor, but its frequent association with the syndrome is strong evidence that alcohol probably brings about other conditions which are responsible for or contribute to the clinical situation. It is not plain what the links in the chain may eventually prove to be, but that vitamin B_1 is definitely included in the chain seems to be adequately demonstrated. The immediate relation between the vitamin and the proclivity to hemorrhage, endothelial hypoplasia and associated degenerative changes has not yet been completely analyzed.

The authors' group of 27 cases in Bellevue Hospital in which the diagnosis of Wernicke's syndrome was made provides, so far as I know, a larger mass of clinical material than that available to any other contributor to the literature on this subject and represents the accumulation of only five years. The case histories would seem to justify the diagnosis, there being general symptoms which vary from case to case with the special focalizing symptoms of ophthalmoplegic involvement. The extremely serious character of this clinical picture is shown by the mortality of over 50 per cent. This high mortality is to a considerable extent to be found in the early cases; deaths in later cases apparently were due largely to intercurrent infections and reduced resistance to such infections. When time allowed for the institution and maintenance of appropriate vitamin therapy for a sufficient period, the ophthalmoplegic defects seemed to be cleared up satisfactorily, the other features of the syndrome, such as the Korsakoff embellishments and the peripheral neuropathy, being affected variably by subsequent therapy.

As emphasized by the authors, the essential neuropathologic lesions, consisting of hemorrhages, small degenerative foci, ependymal thickenings and endothelial proliferations, are situated in the periventricular gray matter from the rostral end of the third ventricle to the caudal portion of the fourth ventricle. Clinical evidence implicates peripheral nerves, the spinal cord, the cerebellum and the psychic apparatus.

The occurrence of stupor, confusion and unconsciousness in so many cases in which periventricular and periaqueductal lesions were present coincides well with previous observations that these regions and the hypothalamus are the only parts of the nervous system, except those immediately concerned with life itself, which are intimately associated with consciousness. Clinical, experimental and pathologic observations associate closely the hypothalamus and the periventricular and peri-

aqueductal gray matter. All available areas of the cortex have been removed without affecting consciousness, but no liberties can be taken with the areas under consideration without some alteration of consciousness.

The other question of great importance is what element in the particular regions which are outstandingly involved by this process results in the predilection for hemorrhagic manifestations. Why these lesions are found where they are and similar lesions are not found in other regions of the gray matter or in the white matter is not at once evident to careful consideration. The following factors may have some influence: The periventricular and periaqueductal regions possess a less firm matrix than other regions of the tegmentum or the basis of the brain stem; the ophthalmic nuclei are adjacent to the midline and situated at a maximal distance from the basilar source of the blood supply of the neuraxis; the vessels supplying these parasagittal structures are the longest, and probably the straightest, of those penetrating the brain stem; as suggested by Marburg, these vessels usually arise at right angles from their parent stem, and therefore the possibility of vascular eddies at their origins must be borne in mind. It is difficult to understand why, if these factors have anything to do with the distribution of the lesions, similar hemorrhagic areas are not found in the similarly situated hypoglossal nuclei. The existence of hemorrhagic lesions in the tuberal nuclei and the mamillary bodies would apparently withdraw support from a purely mechanistic explanation for the facts. Although the investigators seem to be more closely approaching an elucidation of many of the aspects of this problem, enough remains to fascinate succeeding generations of serious thinkers.

The authors have probably purposely said nothing about the pathologic evidences shown in these cases, in many of which a necropsy must have been done. I should, however, appreciate a word of explanation.

Only 1 authenticated case of superior polioencephalitis haemorrhagica has appeared in the files of the record room of the Presbyterian Hospital. The patient, aged 66, was admitted on account of gastrointestinal symptoms. He was found to have a gastric carcinoma, and operation was performed on March 23, 1938. Normal convalescence proceeded until April 6, when he suddenly began to have periods of alternating clarity and mental confusion and disorientation; there then appeared marked horizontal and vertical nystagmus, followed on April 8 by haziness of the disks and on April 9 by complete ophthalmoplegia, with no other focal signs. The spinal fluid showed a few red and white blood cells. The sugar content of the blood measured 88 mg., the chlorides 726 mg. and the protein 78 mg. per hundred cubic centimeters. The patient died promptly.

At necropsy large numbers of recent perivascular hemorrhages were observed in the periventricular, tuberal and supraoptic nuclei and in the subependymal zone. There were many ependymal granulations, and endothelial hyperplasia of capillaries was evident; similar changes at the level of the nucleus of the sixth nerve were prominent. The tegmentum and the basis were normal. The periventricular region of the medulla presented the same appearance. There was no evidence of a lesion. The liver presented no definite changes, but the gallbladder showed cholecystitis and subserosal hemorrhages.

It is somewhat difficult to associate satisfactorily this rather acute clinical picture with the pathologic alterations seen at autopsy. It would not seem possible for all of these lesions, including vascular dilatation, and ependymal thickenings, to have developed in the short time between operation, on March 23, and the appearance of the ominous symptoms, on April 6. It may be that nutritional disorders dependent on the effects of the gastric carcinoma may have long antedated the real symptoms and insidiously brought about alterations which became evident through their effects when activated by dietary and other restrictions imposed after operation.

DR. LEO ALEXANDER (by invitation): Dr. Jolliffe, Dr. Wortis and Dr. Fein are the first investigators who have treated specifically part of the Wernicke syndrome; this adds to the record, for Jolliffe and Goodhart obtained the first conclusive results with treatment of neuritis with vitamin B_1. Since Dr. Wortis

and Dr. Jolliffe mentioned the experimental work which confirms their findings so strongly, I should like to show a few pictures of the results to demonstrate the identity of their results with those of the work on animals.

The first slide is a brief schema of the distribution of the lesions in the paramedian nuclei, the mamillary bodies, the periaqueductal gray matter and the vagal nuclei. I agree with the authors that the lesion of which one can be definitely sure is the periaqueductal alteration, while I believe that the clouding of consciousness is due to a paramedian lesion and that the cause is probably indistinguishable from that of other cloudings of consciousness which may occur as a result of cortical lesions. The vagal lesions are interesting. I think their clinical correlate is the extreme tachycardia, and I should like to ask Dr. Wortis whether he has observed this symptom in all the patients who died. From autopsy observations I believe that the lesion in the vagus nucleus can be regarded as a cause of death. I have had a hard time to convince medical examiners, but I have felt so sure of it that I have called this lesion the cause of death in cases in which extreme tachycardia was present.

One word about the complications: I agree that the pure picture is rarely existent in man. In man the cortex frequently appears normal at autopsy, and metabolic interference perhaps resulting from vitamin B_1 deficiency is postulated. In most cases there is an additional nicotinic acid deficiency, which Dr. Jolliffe has well described.

I want to emphasize that Dr. Jolliffe and Dr. Wortis first called attention to the use of very large doses. Criticism of vitamin treatment has been based on the use of too small doses.

Frequently one sees in patients with early alcoholism, even when they do not have symptoms of the Wernicke type, shininess of the shins and sometimes senile hyperkeratosis. This is considered due to nicotinic acid deficiency of long standing, which gives rise to the changes in the skin before those in the nervous system occur.

Dr. Norman Jolliffe: I have nothing to add to Dr. Wortis' presentation except to reemphasize a point brought out both by Dr. Wortis and by Dr. Alexander, that is, that in these cases of nutritional encephalopathy there is almost never a single vitamin deficiency. One sees often in the same person delirium tremens, Korsakoff's psychosis, encephalopathy due to nicotinic acid deficiency and the Wernicke syndrome. These syndromes occur in any combination. One factor in the Wernicke syndrome, the ophthalmoplegia, is due, we believe, to a deficiency in thiamine hydrochloride. Other symptoms, such as the sucking and grasping reflexes, the changing rigidities and often the stupor, respond to administration of nicotinic acid. Just what deficiency delirium tremens represents we are unprepared to say.

A word of warning is that adequate treatment does not consist in giving pure chemical substances. If, for example, one gives thiamine hydrochloride or nicotinic acid only, one is treating only one part of a syndrome that is probably multiple. In the treatment of these patients it must be seen that they receive a complete diet with vitamin concentrates plus the specific vitamins if a complete cure is to be expected.

Dr. Herman Wortis: With regard to the mortality rate, we agree that most of the deaths occurred in the earlier cases, in which treatment with vitamins was not carried out. At present we see no reason why any patient with the Wernicke syndrome should die if he is treated early enough and if there is not a complicating infection which in itself might be sufficient cause for death.

Is the hypothalamic region the only portion of the brain concerned with consciousness? I can only repeat that our data on this score are incomplete, and we see no reason to accept the hypothesis on clinical evidence.

Regarding the predilection of this disease for the gray matter, I can only suggest that the gray matter has a higher metabolic rate than the white matter. This, of course, does not explain the selective histopathologic involvement of the midbrain.

Autopsies were obtained in only 3 cases, and in all these there were lesions typical of the Wernicke syndrome.

One point concerning gastric cancer is worth stressing. In 1931 Neuburger noted that this syndrome would be seen more frequently in the terminal stages of gastric carcinoma if patients with such a condition were examined more carefully when they sank into terminal stupor. He rightly pointed out that in cases of this malignant condition the terminal stupor frequently did not receive the consideration it deserved, because of the general hopelessness of the illness.

The value of Dr. Alexander's work became increasingly apparent as he presented the material. We feel that he has made a great contribution to the problem.

With regard to the relationship of the dorsal vagus nucleus to tachycardia we have little to say. Practically all of our patients had tachycardia, and since most of them had fever and increased psychomotor activity, we found this particular sign difficult to evaluate. Dr. Alexander mentioned 1 case of Wernicke's syndrome in which the condition progressed to a Korsakoff picture and the patient then recovered. This was true also in 1 of our cases. At present we do not know where the Korsakoff picture fits in this group of encephalopathies of nutritional origin, but we feel that our evidence is fairly good that the Korsakoff syndrome is not a vitamin B_1 deficiency.

DR. LEON H. CORNWALL: In the light of the discussion of Dr. Riley and the length of time the patient he described had been ill, would Dr. Wortis or Dr. Jolliffe care to express any opinion as to the minimal time necessary for a deficiency of this nature to develop?

DR. HERMAN WORTIS: That would depend on the completeness of the deficiency. The more complete the deficiency, the shorter the time it would take to produce a Wernicke picture. Factors like fever, activity, vomiting, the condition of the gastrointestinal tract and diet all would have to be considered before Dr. Cornwall's pertinent question could be answered.

DR. NORMAN JOLLIFFE: The man had carcinoma of the stomach. Undoubtedly he had a quantitative inadequacy for time. An operation, I judge a gastric resection, was then done. He was probably fed chiefly by the intravenous route. We can throw our patients into an encephalopathic state in three to five days by such dextrose therapy. I am not surprised to hear that a Wernicke syndrome developed in Dr. Riley's patient.

Intellectual Psychotherapy. DR. GREGORY ZILBOORG.

With the exception of psychoanalysis, we have no systematized and scientifically ordered psychotherapy. There have been numerous rather grossly empiric attempts, by various nonmedicamental methods called psychotherapies, to effect curative results and to formulate theories. These attempts—suggestion, hypnotic influences, faith healing, moral persuasion, combinations of drugs and verbal persuasions, implied or actual threats—are as old as the history of medicine. Yet it is as difficult today as it has been for many centuries to assess the accuracy of psychotherapeutic procedures and results.

Roughly, all existing therapies may be divided into two groups. The first is the group which uses direct emotional pressure, embracing hypnotism, faith healing and moral persuasion. In all of these therapies the principle of medical, self-assertive command is in the foreground and the patient is pressed to mend his ways. The second group utilizes purely intellectual processes, rather than moral issues; the physician strives to make the patient "understand himself." This group assumes the existence of so-called common sense, while the patient's obsessional thoughts, or his compulsion behavior, are admittedly in conflict with common sense. Any attempt to apply the purely intellectual methods of psychotherapy is bound to enhance the psychopathologic process, which is compulsive, obsessional or conceptual thinking.

Man has always overestimated his intellect, however, and intellectual tendencies prevail in psychotherapy more than in any other field of medicine. There are

numerous nonmedical incursions in the field of psychopathology, the outstanding example of which is to be found in the increasing influence of semantics on the minds of not a few psychiatrists.

It is not therapeutic nihilism which should be espoused, but a psychotherapy as yet to be born which will take into consideration the human personality as a psychobiologic unit. The psychotherapeutist will have to relinquish his tradition of overestimating the intellectual potentialities of mankind. It is not only scientifically untenable to limit one's self to intellectual considerations alone; it is actually injurious not to discard completely the apparent intellectual aspects. The most important contribution of psychoanalysis is the discovery of psychologic constellations which are more dynamic and controlling than so-called pure intellect. As far as the patient-physician relationship is concerned, only the affective, repetitive reactions of the patient described by Freud as transference phenomena are capable of yielding a real clue to the pathogenic factors involved and to the therapeutic directions to be taken. Psychoanalysis should not be the only psychotherapy recognized as valid—it leaves a great deal to be desired—but whatever approach is used is bound to be but an unscientific groping producing therapeutic uncertainty and medical disappointment unless the dynamics of transference are thoroughly understood by the therapeutist.

DISCUSSION

DR. PAUL SCHILDER: It is rather difficult to discuss Dr. Zilboorg's essay since it deals chiefly with theories and there is little factual material. I shall try to discuss it by asking first: What is intellectual psychotherapy? Dr. Zilboorg fights against a psychotherapy in which the psychotherapeutist forces the patient to do something without knowing what the patient is like and what he forces him to do. It is true, furthermore, that he should not stir up emotions in a patient without knowing what he is doing. It is true that the analyst must take into consideration his own emotions and the emotions of the patient, but he cannot do that without knowing what he is doing. When a patient is very sleepy, when he has been out the night before, he is not able to use his intellect to produce a good association and to understand the interpretation which is given to him. He cannot react with the proper emotions to the analytic situation. As far as I can judge the newer trends in psychoanalytic practice, psychoanalysis has become more and more an active approach to the patient based on knowledge, which in turn is based on associations. The days are past when the analyst could sit behind the patient waiting for him to bring up the correct association. Those who really analyze with a passive technic have been rather disappointed in their results. The intelligence and the "free associations" of the analyst play an enormous part in any analytic treatment. Analysis is an active process. This process is intellectual and emotional in the patient as well as in the physician. This is not very different from what Dr. Zilboorg has stated.

I wonder whether the therapy which Dr. Zilboorg condemns should not be called "pseudointellectual" psychotherapy. The intellect has an enormous power. It flows in the patient and in the analyst from deep emotional sources. Without emotions there is no intellect, and every modern logician emphasizes that intellect cannot be separated from emotions. In the formulation of Freud (Ueber einen Fall von Zwangsneurose, in Gesammelte Schriften, Vienna, Internat. psychoanalytischer Verlag, 1925), thinking is a tentative action performed with comparatively small quantities of energy. The intellect is a testing process. Analysis is a testing process guided by the intellect and by the emotions of the analyst. Dr. Zilboorg himself has said that the use of intellect in psychotherapy is of great value. The modern concept of the ego in psychoanalysis is based on the appreciation of reality testing, of which intellect is an integral part. Nevertheless, the relation of the analyst and the patient is deeply emotional. Accordingly, the analyst has also to test his own emotions. Activity in psychotherapy and in psychoanalysis has become more and more important. The active treatment recommended by

Ferenczi (Weiterer Ausbau der "aktiven Technik" in der Psychoanalyse, *Internat. Ztschr. f. Psychoanal.* **7**:233-263, 1921) insists that the analyst should know about the patient before starting active psychotherapy.

I do not quite see the connection between the problem of intellectual psychotherapy and social recovery. The term social recovery denotes a more or less practical connotation and is not well circumscribed. There are many patients who are incompletely cured and cannot be cured completely.

DR. A. A. BRILL: The subject is not as difficult and not as "intellectual" as one has been led to think by Dr. Zilboorg's paper and Dr. Schilder's discussion. To be sure, psychotherapy presents all the problems that they have enumerated, but one must not forget that, regardless of theories, the psychotherapeutist is a physician, who has to do something for the patient. To inject philosophy into psychotherapy is interesting, but not helpful. What are we to do as psychotherapeutists? Freud taught that any psychotherapy which helps is good. In this respect Freud was not prejudiced in favor of psychoanalysis. I agree with Dr. Schilder that Freud himself was not as passive as the term implies. Naturally, it is best to have training in psychotherapy and to know what one is doing. I feel that psychoanalysis is the best form of psychotherapy. It is not only efficacious but also revealing and instructive, but I have also used other forms of psychotherapy. Let me give an example anent Dr. Zilboorg's idea that mere social adjustments of patients are not enough, that they may even do harm. In many cases that is all we can do, and in this respect we are no different from other medical men.

In 1909 a young man came to the Vanderbilt Clinic with the following obsession: He knew a girl in his block who was not a nice girl. He had never had anything to do with her. Some one told him that she was pregnant, and he was obsessed by the idea that he was responsible for it. He told me that he knew he was not responsible, and yet he could not dismiss that thought from his mind. He had even talked to his priest, who consoled him and forgave him because he was really not guilty of anything, but the obsession stuck to him. I told him what he had already been told by his father confessor, that he was not responsible and to forget it, and as this suggestion was not efficacious, I hypnotized him and commanded him not to feel responsible for what he had not done. He returned in a week and told me that my treatment was marvelous, that he felt fine. Years after I had left the Vanderbilt Clinic, he consulted me in my office with regard to an obsession of a different kind. This time I learned that he had been married, had four children and lived the life of a well behaved, good citizen, working in one of the city departments. I again hypnotized him, with the same result. That was all he wanted me to do. I saw him two weeks ago at the World's Fair. He was there with his whole family, and it was a real pleasure for me to see that socially adjusted family, for whom I had done very little. If he had had plenty of money, I might have analyzed him, and perhaps have achieved similar results. But I said to myself: "That man needs the force of a visible father to impress him. Undoubtedly the good priest tried to give him that, but he was not forcible enough." So I gave him *Schreckhypnose,* which seemingly helped him to get along very well. To be sure, I did not do any psychoanalysis in this case, but I did as much for him as for any other patient who asked for help. Theoretically, Dr. Zilboorg gave a very good paper, but factually he did not tell anything new. All know that the practice of psychotherapy is individual. Everybody practices his own psychotherapy, whether he is trained as a psychoanalyst or as any other type of psychotherapeutist, but the main thing to remember is to help the patient.

DR. GREGORY ZILBOORG: I deliberately pointed out the vicissitudes of psychotherapy in practice, and I wanted to show the importance of the emotional factors, which are not taken into consideration because most psychotherapeutic approaches are intellectualistic, if you will, instead of intellectual. To underestimate the importance of the dynamics of transference, to confuse social adjustment with social recovery, is not right. I do not oppose any type of psychotherapy except

the type of intellectualistic psychotherapy which Dr. Brill is apparently willing to accept. I wish I could accept with such benign simplicity his belief, namely, that the practice of psychotherapy is "a matter for each individual." It is not a matter for each individual. It must become systematized by those who are trained for it, or it is outside the pale of a medical discipline. That is why I made a brief historical survey of the situation, in order to impress on those who followed my thought the fundamental idea that in psychotherapy today, as for many centuries, one is still using one's own private talents and endowments without subjecting them to scientific evaluation. I do not oppose activity, nor do I support it.

CHICAGO NEUROLOGICAL SOCIETY

HARRY PASKIND, M.D., *President, in the Chair*

Regular Meeting, Oct. 17, 1940

Neurologic Significance of Platybasia. DR. W. A. GUSTAFSON (by invitation) and DR. ERIC OLDBERG.

This paper was published in the December 1940 issue of the ARCHIVES, page 1184.

DISCUSSION

DR. BEN W. LICHTENSTEIN: This paper is interesting in that in 4 of the 5 cases two distinct pathologic conditions were presented, namely, a bony anomaly, involving particularly the base of the skull about the foramen magnum and in some cases the upper cervical vertebrae, and a syringomyelic condition of the spinal cord. One asks at once whether there is any relation between these two conditions. I believe that at least three possibilities must be considered: first, that the bony anomaly is the primary pathologic condition and that the changes in the nervous system are purely secondary; second, that an embryonal defect in an early formative period resulted in both the platybasia and the syringomyelia, and, third, that the two conditions are independent and the occurrence of syringomyelia in cases of platybasia is pure coincidence.

The first possibility must be strongly considered because improvement in the neurologic condition occurs in some instances after an operative procedure on the bony anomaly. In this respect there is a similarity between platybasia and spina bifida, for the latter frequently results in another disorder of the nervous system, namely, the Arnold-Chiari malformation. The condition described by Klippel and Feil is also frequently associated with changes in the spinal cord, and it may be a link in the chain connecting typical spina bifida with platybasia.

DR. W. A. GUSTAFSON: The question of anesthesia was raised. It usually extended down from the second cervical segment; the most marked atrophy was below that level and in the upper extremities, but the anesthesia usually started at the second cervical segment. Three years ago I saw a case of Paget's disease in which acute syringomyelia developed; the roentgenogram showed definite occipitalization of the first cervical vertebra. No operation was performed, as the condition was associated with Paget's disease.

DR. ERIC OLDBERG: Dr. Lichtenstein has mentioned the possibility of the defect being interdependent, that is, affecting both bone and nervous tissue. There is undoubtedly some truth in his suggestion, but I believe that since patients with this condition improve after relief of the bony constriction it is probable that any previously existing neurologic defect is exaggerated by the additional embarrassment of the bony defect. The results in our cases have been distinctly encouraging, and we feel that there is now something better than mere roentgen therapy or drainage of the cystic cavity to offer many of these patients with cervical syringomyelia.

DR. PETER BASSOE: A case which has been reported by Fay was that of a student aged 19. When I saw him in 1936, he presented symptoms that made me think he had syringomyelia. For about four years he had carried his neck stiffly. He had been seen by orthopedists, who found he had fusion of the upper two cervical vertebrae. He had noted that he did not feel hot and cold water in the shower. A carbuncle developed on the neck and then partial paralysis in both arms, and there was loss of pain sensation. The whole picture was one of syringomyelia. I saw him again about six months later, and the picture had changed. Weakness of the legs and other symptoms had developed that made the condition look like multiple sclerosis.

Fay has pointed out that the condition has been mistaken for both multiple sclerosis and syringomyelia. Fay and Chamberlain demonstrated well the deformity of the upper cervical vertebrae. It was my impression that in the beginning Fay attributed much of the trouble to dilated veins and phlebitis and the deformity of the spine and later to deformity of the foramen magnum. Operation in 1937 resulted in pronounced improvement, and the boy was able to go back to college. He had a slight relapse, but so far as I know he is well now. I think the men who have worked out this condition deserve gratitude.

Paralysis of Conjugate Lateral Movement of the Eyes in Association with Cerebellar Abscess. DR. PAUL BUCY and (by invitation) DR. THOMAS A. WEAVER.

In a series of 7 verified cases of cerebellar abscess seen at the University of Chicago Clinics, we have noted paralysis of conjugate lateral movement of the eyes to the side of the lesion in 3. We wish to present this sign as a valuable aid in the diagnosis and localization of the condition, which is often a perplexing problem. Previously this sign has attracted little attention, although it has been mentioned by Rowe, Meyers Ramadier, de Stella and Bucy.

The 3 case histories are presented. In each case there was paralysis of conjugate lateral movement of the eyes to the side of the abscess and in 2 spontaneous conjugate deviation of the eyes away from the side of the lesion as well. The significance of these findings was not appreciated in the first 2 cases, and, in the absence of sufficient other localizing signs, an extensive suboccipital craniectomy was performed for exploration of the posterior fossa. In the last case the abscess was exposed and drained through a small trephine opening in the suboccipital region on the correct side.

The clinical significance of the sign is discussed. First, there is the possibility of lateralizing the lesion within the cerebellum, since both the literature and our own experience are in agreement that the paralysis of conjugate lateral movement of the eyes produced by a lesion in the posterior fossa is always ipsilateral to the lesion. Second, the possibility arises of localizing the lesion to the cerebellum. In this the sign is not so positive, but nevertheless is of great significance when evaluated with the history and the other findings at hand. Often the diagnosis lies between abscess of the temporal lobe and cerebellar abscess secondary to disease of the middle ear. To our knowledge, paralysis of conjugate gaze has not been reported in association with abscess of the temporal lobe. Differentiation from the commonly transitory paralyses associated with lesions of the frontal lobe and from pontile lesions should be possible. Third, there is the possibility of differentiating abscess and tumor. In our experience, when present in association with an expanding cerebellar lesion, paralysis of conjugate gaze is preponderately in favor of abscess and, when considered in conjunction with the history and the other findings, is usually conclusive.

In summary, 3 cases are presented to illustrate the occurrence of conjugate deviation of the eyes away from the side of a cerebellar abscess with paralysis of conjugate gaze toward that side as a valuable aid, when present, in the diagnosis and localization of cerebellar abscess.

DISCUSSION

DR. PERCIVAL BAILEY: I have nothing to add about the conjugate lateral movement of the eyes, but I should like to note the fact that all the patients recovered, even after streptococci had been spilled rather freely in the subarachnoid space. I think that is good evidence of the value of sulfanilamide. The prognosis of cerebellar abscess is generally considered to be poor.

Importance of Bilateral Calorization in Diagnosis of Tumors of the Brain.
DR. HANS BRUNNER (by invitation).

DISCUSSION

DR. R. P. MACKAY: This interesting presentation leaves little doubt that bilateral calorization gives pathologic findings in cases of infratentorial disease. Whether in the face of such findings one is justified in assuming the presence of a tumor is not so clear. What results does the procedure give in "normal" patients, particularly in patients with other diseases of the cerebellum or of the vestibular mechanism? Until the author's findings are properly controlled by studies on normal persons and on patients with other types of infratentorial disease one must be on the lookout for false positive results.

DR. JOHN FAVILL: I should like to make a suggestion concerning vertical nystagmus, which Dr. Brunner said was unexplained. He probably believes, as I do, if not in current, at least in a slight shift of endolymph, as the cause of nystagmus. If he accepts the current-muscle mechanism which I have previously described, the following explanation might account for the reaction: Suppose the anterior vertical canals are abnormally placed so that their planes are almost perpendicular to the midline and the posterior vertical canals almost parallel to it. I know such abnormalities do occur, just as do wide variations in the shape and size of sinuses. In such a case the anterior vertical canals would be more accessible to the cooling effect of injection, which could conceivably start the necessary current combination. The interesting thing is that in such a situation, in contrast to that for horizontal or rotary nystagmus, bilateral simultaneous calorization would not produce antagonistic effects but rather a cooperative action resulting in vertical nystagmus with the quick component upward.

DR. HANS BRUNNER: In unilateral calorization one ear is irrigated and after a period of five or ten minutes the other ear is irrigated. In bilateral calorization the two ears are irrigated simultaneously.

With reference to Dr. Mackay's discussion, I have always considered the otologic examination of neurologic patients as an auxiliary only, the definite diagnosis being the task of the neurologist. In that respect otologic and ophthalmoscopic changes are of like significance. The finding of a choked disk does not permit definite diagnosis of tumor of the brain, and a positive result in bilateral calorization does not permit definite diagnosis of a tumor of the posterior fossa. However, such findings corroborate neurologic symptoms pointing to a tumor in the posterior fossa.

The finding of a different degree of labyrinthine excitability on each side is, per se, by no means characteristic of tumor of the brain. That difference is found in all atrophic diseases of the inner ear, in disseminated sclerosis, after injuries to the head, in arteriosclerosis of the posterior fossa and in many other conditions. However, it might corroborate the diagnosis of tumor of the brain in connection with other neurologic and otologic findings.

Systematic examination by bilateral calorization in cases of diseases of the brain without increased intracranial pressure has as yet not been established. Thus Dr. Mackay's question cannot be answered. One must consider the difficulty of examining patients with such conditions, since the mortality rate is far below that of tumor of the brain. One does not often have an opportunity to compare the findings of bilateral calorization with surgical or autopsy evidence in order to

evaluate bilateral calorization. Furthermore, many of these diseases involve a wide area of the brain, so that bilateral calorization is not required or its interpretation is difficult.

I am not prepared to say whether or not the vertical nystagmus obtained in normal persons after bilateral calorization is due to irritation of the posterior semicircular canals. There are two difficulties: First, the posterior semicircular canals are deeply embedded within the temporal bone, and consequently they are barely reached by the stimulus of the cold water. Second, if the vertical nystagmus is a normal response on the part of the posterior semicircular canals it is difficult to understand why this nystagmus is rarely found in normal persons.

Immediate and Late Effects of Intrathecal Injection of Iodized Poppyseed Oil. Dr. A. W. Marcovich and Dr. Charles M. Jessico (by invitation) and Dr. A. Earl Walker.

The intrathecal injection of iodized poppyseed oil is followed in slightly more than half the cases by a mild fever of short duration and less frequently by headache and aggravation of previous symptoms. The cells and protein content of the spinal fluid are usually increased and may remain so for several days. Fatal reactions, although rare, have been reported.

A follow-up study of 47 cases an average of three and one-half years after the intrathecal injection of iodized oil reveals that permanent clinical ill effects are extremely rare. Although the iodized oil slowly becomes fixed in the sheaths of the spinal nerves and the caudal sac, it usually produces only mild arachnoiditis with fine adhesions between the arachnoid membrane and the dura mater. If, however, after the injection of iodized oil the dura mater is opened at operation, the iodized oil commonly becomes rapidly encysted by proliferation of the arachnoid membrane. Pia-arachnoid reactions, therefore, would seem to be less likely if the dura is not opened.

Although about one third of 21 patients who have had intrathecal injections of iodized poppyseed oil have a varying number of small globules of iodized oil within the intracranial cavity, none have complained of any symptoms which might be referable to the oil.

DISCUSSION

Dr. Hans H. Reese, Madison, Wis.: Since the medical profession today is too "herniated disk conscious" and therefore too liberal with iodized oil as a diagnostic medium, it should be known what iodized oil does to the cord and to the meninges. My experience with iodized poppyseed oil since 1925 confirms all the statements of Dr. Marcovich and his co-workers. I have not seen any detrimental effects from its use, and I have not observed any caudal conus or peripheral signs. The oil in the caudal region remains fixed in most instances; it can be poured out only occasionally after several months. The fixation of iodized oil in the cul-de-sac depends on the p_H of the spinal fluid; i.e., higher alkalinity saponifies the oil more quickly and permanently. In all cases, traces of iodized oil are found along the caudal nerves in the form of oil buds of varying size, some 1½ to 3 inches (3.8 to 7.6 cm.) distal to the caudal accumulation of oil.

In my opinion, iodized oil should be used only on exhaustion of clinical and laboratory investigative tests.

Dr. George B. Hassin: I understood Dr. Marcovich to say that the iodized oil was found over the spinal roots. It thus arrived there from the spinal subarachnoid space. This proves that escape of the contents of the subarachnoid space, whether iodized oil or spinal fluid, is along the perineurial root spaces. Deery and Van Dyke also demonstrated the presence of iodized oil even farther along the lumbosacral nerves after injection into the subarachnoid space.

Certain substances, such as liquid petrolatum, injected into a peripheral nerve, as done by Japanese investigators, were found in the subarachnoid space of the cord and the brain. The pressure caused by the injection may account for such a retrograde flow in these experiments.

Iodized poppyseed oil produces irritation and adhesions which are not strong enough to affect the nerve fibers unfavorably but are strong enough to interfere with the flow of the oil or of the spinal fluid in the perineurial root spaces.

DR. M. N. WALSH, Rochester, Minn.: I should like to say a word about the technic my associates and I use at the Mayo Clinic. We now employ air myelography in cases in which intraspinal protrusions of the lumbar intervertebral disks are suspected. This has been found by Dr. Camp to be accurate in about 71 per cent of cases. If the syndrome appears typical of protruding disk and the air myelogram shows nothing abnormal, iodized oil studies are then made in most cases. The accuracy of this method, according to Dr. Camp, is about 92 per cent. Our observations confirm the findings of the authors in regard to the absence of any chronic irritation following injection of iodized oil. We have found that only mild transitory meningeal irritation takes place. The occasional exacerbation of pain following injection of iodized oil usually occurs in cases in which there is an intraspinal space-occupying lesion, such as a tumor or a protruding disk and it is probable that the introduction of any other liquid would also produce increase in pain.

DR. A. EARL WALKER: In a few cases the iodized oil has followed the roots of the spinal nerves into the nerves of the lumbar and cervical plexuses. The oil has been reported in the popliteal space four months after intrathecal injection.

We are not advocating the use of iodized oil for myelographic examination. We have been interested solely in determining the immediate and later effect of its injection. We realize it is not an ideal substance, but we have not found a substitute that gives as good or as constant results.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

BRONSON CROTHERS, M.D., *President, in the Chair*

Regular Meeting, Nov. 21, 1940

A Comparative Study of Recovered and Deteriorated Schizophrenic Patients. DR. OTTO KANT, Worcester, Mass.

The results of a comparative study of two groups of 39 recovered and 39 deteriorated schizophrenic patients are reported. Certain general features (acute onset, psychogenic precipitation, presence of clouding, extroversion and pyknic physique) which predominated in the recovered group were infrequent in the deteriorated group. All the recovered patients who had more than one psychotic episode were apparently completely well between their attacks, while those in the deteriorated group, with the possible exception of 2 patients, showed definite signs of defect after their first attack. A comparison of the initial clinical states revealed certain structural differences between all the clinical features which occurred in both groups and superficially appeared identical. While coherence and uniformity of the abnormal production were distinctive features of the recovered group, lack of coherence, autism and bizarreness characterized the early pictures of the deteriorated group.

DISCUSSION

DR. ALFRED HAUPTMANN: Did the schizophrenic patients who made a good recovery have what one might call a more periodic course? I found that the rate of recovery was best among the patients who had periodic attacks. I also came to the conclusion that the patients made a real recovery and that they did not have manic-depressive psychoses but suffered from true schizophrenia, with several attacks.

DR. WILLIAM HUGHES, Providence, R. I.: With regard to general emotional maturity, what tests did you use and what tests proved important?

DR. IVES HENDRICK: I wonder whether the study was made from case records and whether it is possible that the records are far less carefully made for the type of person who is going to become deteriorated.

DR. OTTO KANT, Worcester, Mass.: Fourteen of the 38 patients who recovered had more than one attack, and there were 3 patients in this group of whom one could speak as having a periodic return of attacks. In the deteriorated group there were only 5 patients who had more than one attack.

The question whether or not all of the recovered patients had "true" schizophrenia is difficult to answer precisely, since it is not yet known what "true" schizophrenia is. Conventionally, the patients are, and were actually diagnosed as, schizophrenic. It was the chief purpose in these studies to find out a little more about what schizophrenia is and what its limitations are by comparing the findings in prognostically different groups of patients. By this means it was attempted to obtain a new basis for differentiation of schizophrenic pictures into more meaningful entities.

As to emotional immaturity: I did not use any experimental tests. The evaluation was based particularly on the previous attitudes which these patients had shown in times of distress or in solving their problems, and also on a thorough examination of the patients and on interviews with their relatives. All patients in both groups were personally reexamined. I spent about two hours with each patient. This also answers the question about case records. In addition to the personal contact with patients and relatives, I tried to obtain all available information concerning the patient. Dr. Hendrick raised an important point: One is usually more interested in patients with whom contact can be established than in those who show early deterioration. I believe, however, that the records at the Worcester State Hospital are fairly complete in every case, since a long social and medical history of the patient is taken on admission, when as yet no one knows whether he will recover or will deteriorate.

The Male Homosexual: Hormonal and Clinical Studies. DR. ABRAHAM MYERSON, DR. RUDOLPH NEUSTADT and DR. I. P. RAK.

In a previous paper read before this society, an abstract of which was published in the transactions of the society (Neustadt, R., and Myerson, A.: Androgen Excretion in the Urine in Various Neuropsychiatric Conditions: A Preliminary Report, ARCH. NEUROL. & PSYCHIAT. **44**:689 [Sept.] 1940) and which is now appearing in the *American Journal of Psychiatry*, we presented facts which indicated that the true homosexual male had a more or less specific formula for the interrelationship of estrogen and androgen in the urine. This formula may be expressed by the statement that the androgen tends to be rather low but the estrogen is disproportionately high.

Homosexual offenses, like murder, may represent the act of quite different types of persons. First, homosexuality may represent a biologic-psychologic drive, inborn in the person and expressing itself throughout his life history. He is correspondingly averse to heterosexual activities or is incapable of fulfilling them if he tries, and is impelled by passion, and even by love, toward the male.

Second, there may be the person who through some cultural deviation, perhaps due to the pressure of social circumstances, such as desire for financial gain or the inaccessibility of the female, becomes homosexual in conduct, although he is predominantly heterosexual in desire and potency. Such would probably be the case in a good deal of Grecian homosexuality, the homosexuality of low grade persons who satisfy the law of demand by supply and of some persons incarcerated in jails or in institutions of one type or another where females are not to be had. Persons of this group are fundamentally normal heterosexual males.

Third, it is conceivable that there are persons who have both male and female drives from time to time, or even at the same time. This group makes real the immortal quip about Julius Caesar to the effect that he was the husband of all the wives of Rome and the wife of all the husbands.

Fourth, there is a group of passive homosexual persons, having low sexual drives of their own, finding some erotic satisfaction in the situation but possibly in the main merely yielding to stronger wills. These persons would show a low androgen and estrogen excretion and probably would be passive and retreated in many directions other than the sexual. They often have endocrinal disturbances, but probably represent in general persons of low mentality.

Our first group of patients corresponded in the main to the first category, and it was this selected group which directed our attention to the problem. We then undertook to diagnose from examination of the urine alone the condition of some 29 inmates of the Massachusetts Reformatory in Concord who had, for the most part, been arrested for abnormal sexual conduct or who had manifested such conduct during their incarceration.

We were able to select without difficulty and with a very small margin of error the overt, predominantly active, homosexual male without any heterosexual drive. These showed high estrogen and low androgen values. There were several patients in whose cases the quantitative determinations showed normal androgen and estrogen values, or at any rate a normal interrelationship. These were for the most part heterosexual persons who were homosexual through deprivation or whose homosexuality represented a burst of sadism. Some of the patients of this group were not homosexual at all, but the urines had been sent to us for examination together with those of homosexual patients to see whether or not a differentiation could be made. There was a third group with low values for androgen and estrogen who represented immature persons or those with endocrinal deficiencies. These corresponded to our fourth group, namely, persons with low sexual drive who were passively homosexual.

It must be stated at this point that we cannot always separate the urines of males and of females by the chemical evaluation of hormones. A specimen which was inadvertently submitted as that of a man and was diagnosed as that of a homosexual male turned out to be that of a woman. We have not made an intensive study of the hormonal levels in females, particularly because of the great difficulty inherent in such a program, since the quantities vary throughout the estral cycle. However, it may be stated that in general the hormonic level of the female tends to be like that of the homosexual male, although much more work is needed to establish this point.

DISCUSSION

DR. ROY HOSKINS: Such an investigation as this is beset with difficulties from every direction. In the first place, sexuality is multiply determined. The male and female chromosome patterns differ from the time of fertilization, and hormone factors are superimposed on the genetic matrix. Therefore, various anomalies can arise. The social factors which Dr. Myerson speaks of are important and may run counter to the hormone situation. It would be much simpler if one were dealing with lower forms. Twenty-five years ago Steinach showed in guinea pigs that sex reversal is easily producible by combined castration and gonad grafting. In fowls Domm showed that removal of the ovaries may be followed by regeneration of either ovaries or testes, regeneration of the latter giving rise to sex reversal. However, even in animals homosexual behavior can be elicited by "social" factors. Normal male rats excited by nearby rutting females will engage by choice in coitus with females but if only male rats are available will go through mating behavior with them. My associates and I have been interested in the study of what could be done to rectify the homosexual situation by the use of androgen, estrogen and gonadotropin. There is not much evidence so far that one can do anything effective. One of our subjects is thoroughly masculine in the possession of large normal genitals but in every other respect is a "perfect lady." He wears feminine clothing as far as the hospital will permit and is interested in designing women's clothes. He presents the most thorough-going homosexual state that I have ever seen. He has been given

several preparations of androgen, estrogen and gonadotropin. None has made the slightest difference in his personality, temperament or behavior. My feeling is that endocrine factors are probably important in homosexuality but that the primary hormonal situation is often overlaid with confusing factors. What is needed more especially at present are better methods for identification of the "sex hormone steroids," all of which are similar chemically but behave differently when injected into animals. For the most part, the actual hormone titers in the blood cannot be determined, hence one is forced to guess what is going on inside the body by what is being excreted. The reports by Dr. Myerson and his co-workers check well with the recent report of Glass, who also found a disturbed estrogen-androgen ratio in homosexual males.

Dr. Isador Coriat: From a purely descriptive point of view the social history of homosexuality has been interesting and illuminating from the time of the Greeks up to the middle of the nineteenth century. But it is only since the beginning of the twentieth century that there has been any real psychologic insight into the situation, and then only after the psychosexual development of normal persons began to be understood. There is no normal, or so-called normal, person who is either 100 per cent male or 100 per cent female. For instance, every normal male has certain female components in his makeup, both physiologically and psychologically, and vice versa. The same is true of the homosexual person; there is no such thing as a person who is 100 per cent homosexual. The homosexual person differs from the normal person not in his instinctive drives, but only in his object choice. The patients who come to me for therapeutic help naturally have represented the more severe variety, in whom there have developed conflicts and feelings of guilt concerning their fantasies and sexual object drives. In none has there been evidence that the patient was completely homosexual. The attitudes in the male, for instance, showed certain female components in behavior, fantasies and dreams. These patients, therefore, so far as psychologic makeup was concerned, were similar to so-called normal persons, except that the homosexual makeup was more predominant in them. Biologically, it was pointed out some fifteen years ago by Lipschutz, in his work on internal secretion of the sex glands, that in some cases homosexuality can be considered a condition of intersexuality in the psychosexual behavior. I believe that homosexual impotence is not organic, but is a psychologic reaction produced by unconscious guilt components.

I should like to ask Dr. Myerson what he would expect to find in cases of transvestitism or of delusion formation, such as in the Schreber case, in which the patient felt that he was being transformed into a woman? It is interesting to see that Dr. Myerson's chemical investigations have confirmed all the psychologic work that has been done on homosexuality in the last four decades and has put it on an experimental basis, but it must be emphasized at the same time that the purely psychologic interpretation of these problems has long been known.

Dr. Abraham Myerson: The difficulties of this approach are great. First, the methods are crude; second, the tests are made on the urine and do not reveal the situation in the blood, and third, the results do not accurately represent the substances which are actually specific for males and for females.

Dr. Coriat's remarks leave me with mixed emotions. We kept away from any psychologic relations in our study of the hormones in the urine, and we believe that the physiologic and the psychologic aspects of the problem have nothing to do with each other.

It is important to find that childhood is relatively hormoneless and sexless and that all psychoanalyses which have shown the existence of sexuality in childhood must be based on thin air, since they have no hormonic background. In persons with paranoia or alcoholism who are thought to be homosexual there is no change whatever in the relationship of the hormones.

There is no such thing as a completely homosexual or heterosexual person. The male and female are similar in many outward respects, such as the breasts.

Likewise, the androgens and estrogens are closely allied chemically. Both the male and the female have both. There exists a difference only in the quantitative relationship.

Transvestitists on the whole showed normal amounts of androgen. It seemed to us that they put on female clothes to get male desire, and that their behavior did not represent homosexuality.

As to delusion formation: We have had no cases in which the patient thought himself transformed into a woman. As to the statement that more has been learned about the sexual life from the psychologic than from other points of view: I prefer to rest on the uncertain, but more or less objective, grounds of hormone analysis rather than on any other set of facts.

General Psychiatry: A Point of View. Dr. Earl D. Bond, Philadelphia.

What the center of psychiatry is will be settled not by psychiatrists but by patients. From the patients' point of view the center is where most patients can most quickly receive greatest help: it is the psychiatry practiced in large (chiefly public) hospitals and clinics. It has certain interests: "the day by day solicitous observation and care" of thousands of patients; the compilation of life histories; the record of bare fact and recognition of uniformity; the testing under control conditions of new therapies, and the use of temporary theories.

In one direction from the center so defined lies psychoanalysis, a place for the testing of more ambitious theories and for deep and intensive studies on a comparatively few patients. When discoveries come which might be useful in a wider and more superficial field, psychoanalysts should turn toward the center and there seek the limits of their truths.

In another direction lie investigations of the medical sciences into the functions of the body. They have the advantage of objectivity and the disadvantage of the great gap between simple measurements and a complex organism. Laboratory workers must turn toward the center to find in the clinical field the limits of their truths.

President Lowell has said, in his "Conflicts of Principle," that one does not need under pressure to adopt one of two opposite ideas; one can choose both, one at a time. Psychiatry may advance "by the overaccentuation of first one and then the opposite principle."

It may be that psychoanalysis and laboratory studies will prove to be contradictory but, in Mr. Lowell's word, conjugate principles; that is, neither will have universal application. If so, they will both spread into central psychiatry in search of their limits. Such an outlook seems a happy one.

Book Reviews

Psychiatric Dictionary. Leland E. Hinsie and Jacob Shatzky. Price $10.50. Pp. 559. New York: Oxford University Press, 1940.

This dictionary is an important adjunct to psychiatric literature inasmuch as it is the first dictionary of its type since the one of D. Hack Tuke, in 1892. To be sure, R. H. Hutchings' "Psychiatric Word Book" has become available since this time, going through five editions, the last of which appeared in 1937, but the definitions in this handy little volume were exceedingly short and had little descriptive material. In the new psychiatric dictionary there are some 7,500 title entries and the authors have been careful not to duplicate any of the words given by Howard Warren in his "Dictionary of Psychology," published in 1934.

The psychiatric dictionary is made up of psychiatric terms, and it is important to note that all definitions of terms are given from an exclusively psychiatric point of view. Unless this is realized the reader may discover extreme narrowness in definitions of certain words which are utilized in other fields besides psychiatry. The authors have also given some attention to allied fields, such as clinical neurology, constitutional medicine, genetics and eugenics, mental deficiency, forensic psychiatry, social service, nursing and occupational therapy. It is regrettable that they did not, however, include also words from the field of neuropathology, some of which are of considerable importance to psychiatrists. The dictionary also introduces a number of words used for the first time in English dictionaries, particularly those dealing with sexual aberrations and religious manias, such as "skoptsy," "miryachit" and "Hinkemann." In addition to the use of new words, the dictionary contains a great number of obsolete terms which are of considerable value in reading of ancient literature; e. g., "In the 17th century, catalepsy was also called catoche, catochus, congelatio; and by Hippocrates, aphonia; by Antigenes, anaudia; by Coelius Aurelianus apprehensio, oppressio; and also by some apoplexia cataleptica, detenio; encatalepsis; prehensio, comprehensio, deprehensio.'" In addition, the dictionary has an excellent liberal system of cross references, so that terms may be found under either their technical names or their popular English equivalents. For example, the various types of phobias are listed under "fear" as well as under the various Greek terms. This dictionary gives, easily, one of the longest lists of phobias, and any student fond of such terms should be delighted with it.

As in all new works, of course, certain of the terms are somewhat ambiguous and could be considered somewhat deficient, particularly if viewed from any but a purely psychiatric viewpoint. The definitions are frequently given an encyclopedic treatment, and generally an analytic approach predominates. This approach is excellent when the term is of psychoanalytic derivation but falls short when philosophic or neurologic meanings are also of value. It would seem that the definition of psychiatry, "the science of curing or healing disorders of the psyche," is unnecessarily limited in its scope and that the definition of reality, "In psychiatry the term means the whole of the objective world, embracing all that may be perceived by the five senses," is inadequate from a philosophic or a neurophysiologic point of view. The neurologic section might also be extended—for example, the definition of epilepsy, which is given in part as: "Genuine epilepsy is so called in order to convey the impression that, like other psychogenic mental states (e. g., schizophrenia, manic-depressive psychosis, the psychoneuroses), so far as is known, it is not caused by organic disease or anomaly, but is best understood in the terms of the psyche," would be inadequate as regards constitutional, hereditary and neurophysiologic factors. These points are rather fine discriminations, and in view of the fact that the book was written primarily from a psychiatric point of view and for use chiefly by psychiatrists, psychiatric social workers, psychiatric nurses and others connected specifically with the psychiatric field, they are perhaps not of great significance.

The book supplies a needed tool in psychiatric work and, if its specific viewpoint is borne in mind, should be of considerable value to all workers in the field of psychopathology.